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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 24 1959

A PHYSIOLOGICAL APPROACH TO THE PROBLEM OF GENERAL ANAESTHESIA AND OF LOSS OF CONSCIOUSNESS*

BY

W. FELDBERG, M.D., F.R.S.

From the National Institute for Medical Research, Mill Hill, London

To have to prepare a lecture is a pleasant and effective way of being forced to learn about a subject. When I was approached to give this lecture, I was caught in a mood where I felt that I really ought to make an effort to find out what is known about what I would call the fundamental problem of general anaesthesia. I required this knowledge for my own experiments.

When we anaesthetize animals, human beings included, we do so in order to achieve a condition in which consciousness is lost. How is this condition brought about, and what is the physiological basis of loss of consciousness? This, in my opinion, is the fundamental problem of general anaesthesia, and this is the problem I am going to deal with.

William James (1892) said that everyone knows what consciousness is until he tries to define it. I shall not try to do so. A definition sufficient for our purpose is the one given by Stanley Cobb (1948). Consciousness is "awareness of environment and of self." If we are not fully aware either of environment or of self we have some degree of unconsciousness, and the same applies to conditions in which we are aware, not of environment, but of something different, as in dreams.

There is no need to define unconsciousness. We all know what it means. It is the experience we cannot experience, but which we all pass through, every night, when we fall asleep. It is the experience we miss when we faint or are anaesthetized.

Sleep and anaesthesia are two closely related phenomena. The main difference between the two is that we can wake up a sleeping person, or, as Purdon Martin (1949) expressed it: sleep is still a state of unconsciousness into which the messengers of consciousness can penetrate. But even this difference is not absolute and breaks down under certain conditions. Thus the central mechanisms involved in sleep and anaesthesia cannot be so different, and if we were to know what determines the difference between the waking and the sleeping state we should not be far off explaining the unconsciousness of anaesthesia.

The Cerebral Cortex and Consciousness

For a time it was supposed that consciousness was exclusively a function of the cerebral cortex. The unconsciousness which follows head injury, concussion of the brain, was attributed to diffuse cortical damage. That was the view commonly held by neurologists about 40 years ago.

Yet removal of the cerebral hemispheres does not cause loss of consciousness. Such operations were performed on various animals at the end of the last century. And if we look through the older textbooks of physiology we find more detailed accounts of the behaviour of these decorticate animals than in the modern editions. Schäfer (1900), in his textbook, gives an excellent description, including that of the famous decorticate dog of Goltz. In 1892 Goltz had succeeded in removing both cerebral hemispheres in three successive operations and in keeping the dog alive for 18 months after the final operation.

The animal was able to walk in a perfectly normal fashion; in fact, for the greater part of the day it walked restlessly up and down in its cage. But at night it would go to sleep, and it curled round in the manner normal to dogs. When awake it reacted to a loud sound or to a bright light by shaking its ears, or by shutting its eyes and turning its head away, and when its skin was pinched it snarled or barked, or turned round to bite at the hand, but in a clumsy manner. During the first few months it had to be fed by placing food at the back of its mouth; later it took food itself provided its head was placed over the dish containing the food. When meat was rendered bitter by quinine it was ejected with movements indicating dislike. There was, however, no sign of recognition of persons or other dogs, no sign of fear when threatened or of pleasure on being stroked or spoken to. The dog never wagged its tail. There was no sign of memory. For instance, when the dog was taken out of the cage, which was the normal sign for feeding, it invariably resisted, barking loudly, biting, and struggling vigorously. Thus removal of the hemispheres had produced loss of all understanding, intelligence, and memory. The condition was that of idiocy but not of unconsciousness. In fact, the dog had periods of sleep and wakefulness, of unconsciousness and consciousness, although the content of its consciousness must have been enormously different from that of a normal dog.

I also want to describe, because of the close resemblance, the behaviour of human anencephalic and hydrocephalic monsters. In these the cerebral cortex is either absent or has virtually disappeared. Some have survived for 20 years. The late Professor Cairns (1952)

*Lecture given at University College, London, on December 2, 1958, and to the Natural Sciences Society in Amsterdam on February 11, 1959.

described the behaviour of what he called the human brain stem and thalamic "preparation." "It sleeps and wakes; it reacts to hunger, loud sounds, and crude visual stimuli by movements of eyes, eyelids, and facial muscles; it may see and hear; it may be able to taste and smell, to reject the unpalatable and accept such food as it likes; it can itself utter crude sounds, can cry or smile, showing displeasure when hungry and pleasure, in a babyish way, when sung to; it may be able to perform spontaneously crude movements of its limbs." Again, a condition of idiocy but not of unconsciousness. Again, periods of sleep and wakefulness; but what a restriction in the content of consciousness whilst awake. Babies pass through a somewhat similar state.

I want to use a metaphor. A room may contain a chair and a table but nothing else, or it may contain rare pieces of furniture, carpets, and pictures, and the rest of the walls may be covered with books. But at night, when it is dark, this difference is not apparent; it becomes so only when we switch on the light. The contents of the two rooms are as different as the contents of consciousness in the decorticate and the normal dog, in the anencephalic and the normal human being. The contents of consciousness—so far as the higher psychical functions are concerned—are cortical functions, but whether the room is in darkness or in bright light, whether we are conscious or not, that is not a function of the cerebral hemispheres.

Neurological Cases with Manifestations of Loss of Consciousness

And yet as recently as 1950 Jefferson and Johnson could point out that many neurologists still believed that the loss of consciousness from cerebral haemorrhage was caused by general cortical anaemia. Jefferson and Johnson describe a typical case of bleeding from a ruptured middle meningeal artery with the classical sequence of stupor—recovery—stupor. A boy of 14 fell, striking the back of his head on the floor, and, after vomiting, fell asleep, and an hour later did not reply on stimulation; then 15 minutes later he woke up, walked about, and wanted to be left alone, but then he again went to sleep. Within the next hour his condition became worse; he was brought into the operating theatre, and as soon as attempts were made to shave his head he again woke up and spoke resentfully. At operation a large liquid extradural clot was evacuated from the temporal fossa and the spurting middle meningeal artery was coagulated. After the operation, as his bandage was fixed, the boy sat up on the operating table and asked what had happened.

This classical picture of acute compression has become so familiar that, as Jefferson and Johnson say, "surgeons and neurologists have not very often paused to inquire how the loss of consciousness comes about. It seemed to be sufficient to say that the brain was compressed and presumably anaemic."

However, this classical picture of middle meningeal haemorrhage is also produced when the extradural bleeding and compression by the clot occurs in a situation where effects on the cerebral hemispheres can be excluded; it is when the clot is below the tentorium, in the posterior fossa. Jefferson and Johnson describe such a case.

A student stepping off a moving bus, fell backwards, striking the back of his head on the ground. He became unconscious, recovered, but then again went into coma and was deeply unconscious at the time he reached the operating-table. Several burr-holes were made in the skull in search of the clot. His condition became critical, respiration stopped, and artificial ventilation had to be given. On tapping the lateral ventricle the cerebrospinal fluid was found to be under high pressure. Lowering the pressure by aspiration of C.S.F. resulted in a return of respiration but not of consciousness. But when at last, after the bone had been nibbled down towards the foramen magnum, a large clot was removed deep down in the fossa, the patient awoke and became so lively that nitrous oxide had to be given to keep him quiet while closing the wound.

This case strikingly illustrates that consciousness did not return when the general pressure on the brain was lowered, but that it did return as soon as the pressure exerted by the clot on the brain stem was removed.

For many years Jefferson (1938, 1944) had pointed out that the neurologists were wrong in assuming that the cerebral cortex was the seat of consciousness. On the contrary, he said, there is abundant evidence, if observers were only prepared to look for it, that the seat of the disturbance is the brain stem and hypothalamus. Let us look at some of this evidence, starting from the spinal cord and working upwards, making use of the familiar diagram of the brain (Fig. 1).

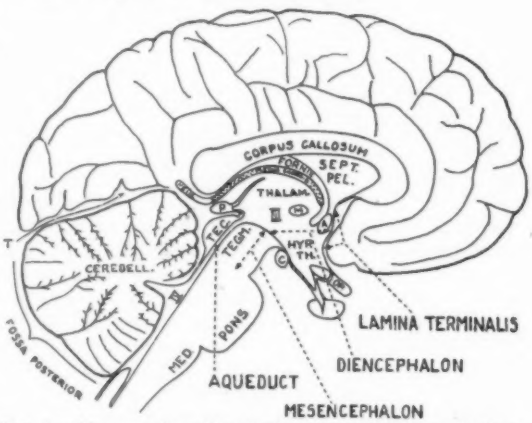

Fig. 1.—Diagram of a mid-sagittal section of the human brain to illustrate some of the terms used. A = anterior commissure; C = corpora mammillaria; Hyp. Th. = hypothalamus; M = massa intermedia; Med. = medulla oblongata; OP = optic nerve; P = pineal body; Sept. Pel. = septum pellucidum; T = tentorium; Tec. = tectum; Tegm. = tegmentum; Thalam. = thalamus; III and IV = third and fourth ventricles. The dotted area below the corpus callosum and fornix is the choroid plexus.

Spinal Cord, Medulla Oblongata, and Pons

Cairns (1952), in his review from which I have heavily drawn, pointed out that tumours of the cervical cord as high up as C 1 do not cause disturbances of consciousness so long as they do not invade the medulla oblongata; if they do, attacks of loss of consciousness may occur. Haemorrhages around the pons and medulla oblongata (Cairns, 1952), or into the substance of the pons (Jefferson, 1944), or into the fourth ventricle (Rosenfeld, 1924) produce deep coma and unconsciousness. And although tumours of the pons are rarely associated with unconsciousness the condition is easily precipitated when the surgeon interferes with the pons in operations for removal of pontile tumours. Well known also is the following accident described by Reichardt (1928).

During puncture of the cisterna a woman lost consciousness because the needle had entered the medulla oblongata. After the needle had been inserted the woman

made a sudden backward movement with her head which drove the needle 2 to 3 cm. deep into the medulla. The needle was immediately withdrawn. At the same moment the woman cried out; then she became motionless, with open staring eyes, and did not respond to loud calls. She remained so for 10 to 15 seconds and then passed through a stage resembling that after an epileptic attack before regaining full consciousness. Afterwards she said that the needle had already been in and was not painful when she suddenly felt a shock run through the right side of her body. Everything went black before her eyes and she saw her whole life rush past her like lightning. Then she lost consciousness; later she heard her name being called from a long way off.

Mesencephalon

I have not been able to find in the clinical literature any reference to lesions confined to the mesencephalon, particularly around the aqueduct, but there is one clinical affection in which the disturbance of consciousness has been associated with the aqueductal grey matter: the sleep-like condition, the somnolence or hypersomnia, of encephalitis lethargica. Economo (1931), who studied this disease during the 1916–17 epidemic, attributed the prolonged sleep to the inflammatory processes in the grey matter surrounding the upper part of the aqueduct, in the zone of transition between mesencephalon and diencephalon.

Diencephalon

Unconsciousness in one form or the other, intermittent or continuous, with or without fits, is characteristic of lesions in the upper brain stem and thalamus—that is, in the diencephalon. The symptoms vary according to the location of the lesion. Unconsciousness associated with a rise in body temperature, hyperthermia, is a sign of acute injury of the hypothalamus. Attacks of unconsciousness resembling *petit mal*, or minor epilepsy followed by major fits, occur with lesions located in the anterior part of the third ventricle and involving the anterior medial parts of the thalamus. Then there is the well-known condition of long-lasting continuous unconsciousness, for weeks or months, where the condition resembles more natural sleep, but where the patient cannot be roused to full wakefulness for any length of time. This condition is characteristic of some tumours in the third ventricle, arising from below the floor of the ventricle. Also in this category belong the sudden attacks of unconsciousness encountered during brain operations under local analgesia during manipulation of the lamina terminalis, the anterior wall of the third ventricle. Cairns describes the case of a child who quite suddenly ceased to respond for a minute when he operated on the lamina terminalis in order to get into the third ventricle; and after the lamina terminalis was opened the child had several short-lasting fits with loss of consciousness. The reverse happens when a tumour in the third ventricle is a cyst and is aspirated under local analgesia through a frontal burr-hole. The stuporous patient is promptly aroused as soon as the cyst is emptied.

Jefferson and Johnson (1950) published a map (reproduced in the upper part of Fig. 2) which gives the area, damage of which leads to depression of consciousness, to hypersomnia, or to coma. The area covers most of the lesions discussed except those in the medulla oblongata and lower part of the pons. The lower map is a more recent one by Jefferson (1958); the area extends more anteriorly to the septum pellucidum and hypocampus. The evidence for this extension rests on cases of unconsciousness from bleeding aneurysms of the anterior cerebral and the anterior communicating arteries.

Epilepsy

There is one clinical manifestation of unconsciousness which has nothing to do with sleep—the unconsciousness of the epileptic fit: the sudden attack of unconsciousness with generalized convulsions, the *grand mal*; or the brief interruption in the stream of consciousness, with or without arrest of bodily movement, the *petit mal*. What brings about the unconsciousness? Records taken from the cerebral cortex during these conditions show what is called "seizure discharges." This abnormal discharge does not originate in the cortex, it only spreads to the cortex, and the spread is from below, from subcortical

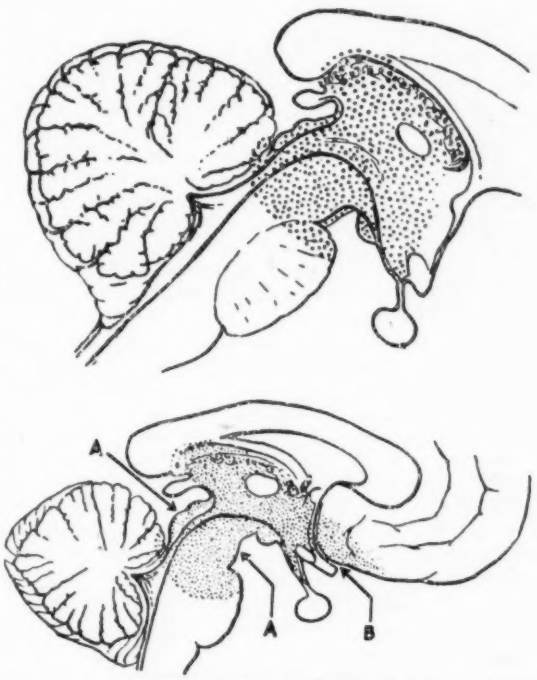

FIG. 2.—Area of brain associated with consciousness. Upper diagram from Jefferson and Johnson, 1950; lower diagram from Jefferson, 1958. Below: Diagram of posterior (A) and anterior (B) critical points in relation to consciousness. Stippling represents area most related to preservation of conscious states.

regions, from what Penfield and Jasper (1954) termed the "centrencephalic system." The unconsciousness results, they say, from an abnormal discharge in the centrencephalic system.

By definition, the centrencephalic system refers to neurone systems which connect both hemispheres and which are located in the central core of the upper brain stem from the thalamus down to the medulla oblongata. We may ask, has a system of such a wide distribution really a meaning from the anatomical or physiological point of view? Whatever the answer—and the centrencephalic system has certainly met with strong criticism on this account—this concept of Penfield and Jasper has given us a new understanding of the mechanism by which unconsciousness is brought about during the epileptic seizure. I particularly want to stress

that unconsciousness is again attributed to the mesencephalon and diencephalon, and, as we shall see, this is also very much the conclusion arrived at by the physiologist.

Approach of the Physiologist to the Problem of Consciousness

Let us start with the E.E.G. By leading off with electrodes either placed on the skull or inserted through a little burr hole made in the bone and resting on the dura, we can record the electrical activity of the cerebral cortex. The record, the so-called E.E.G., differs during wakefulness and sleep. During wakefulness or alertness we record low-voltage fast activity; during sleep, high-voltage slow-wave activity and spindle bursts. This is illustrated in Fig. 3. It is the E.E.G. of a cat. Four cortical records are taken from the anterior and posterior regions of the left and right hemispheres. At the beginning of the record the cat is asleep, and we record high-voltage slow-wave activity and spindle bursts typical for sleep. At the arrow the cat is awakened by a hand-clap, and the arousal causes desynchronization of the high-voltage slow-wave pattern.

High-voltage slow-wave activity is also recorded in many forms of anaesthesia, but there are other effects, varying according to the kind of anaesthesia. They illustrate that many anaesthetics, apart from producing sleep and loss of consciousness, have additional central actions, which can affect the E.E.G. but need not have anything to do with the essential problem of anaesthesia —loss of consciousness.

There is the other question: Is this pattern of cortical activity always associated with loss of consciousness, or can it also occur during wakefulness? It can. Small doses of atropine, hyoscyamine, as well as morphine bring about the typical sleep pattern without producing sleep or signs of impaired consciousness (Andrews, 1941; Cahen and Wikler, 1944; Funderburk and Case, 1951; Wikler, 1952; Bradley and Elkes, 1953, 1957; Bradley and Hance, 1957). However, such dissociation between behaviour and E.E.G. is a rare exception, and it need not prevent us, so long as we keep it in mind, from using the high-voltage slow-wave pattern as a sign signalling loss of consciousness.

Cerveau and Encéphale Isolé

The next step in the analysis of this high-voltage slow-wave sleep pattern we owe to the Belgian physiologist Bremer (1935, 1936), who introduced the so-called "cerveau isolé" and the "encéphale isolé" preparation. These preparations are illustrated in Fig. 4, which is from one of his early papers.

Bremer started from the hypothesis that sleep is the result of suppression of the impulses which usually reach the cortex, or, as he expressed it, results from more-or-less complete deafferentation of the telencephalon—that is, the cortex, the rhinencephalon, and the corpora striata—and that the high-voltage slow-wave activity pattern is the rhythm of the cortex when no longer bombarded by these impulses.

To test this hypothesis he made a transverse section under ether anaesthesia through the brain of a cat at a level between the superior and inferior colliculi but preserving the blood supply to the cortex. The left side of Fig. 4 shows the plane of transection. After the ether has blown off, the head of such a cerveau isolé behaves as if it were asleep. The pupils are slit-like; the eyeballs have swayed downwards, the nictitating membrane, that is, the third lid, is relaxed and usually covers the eye. There is no awakening reaction to smell or light,

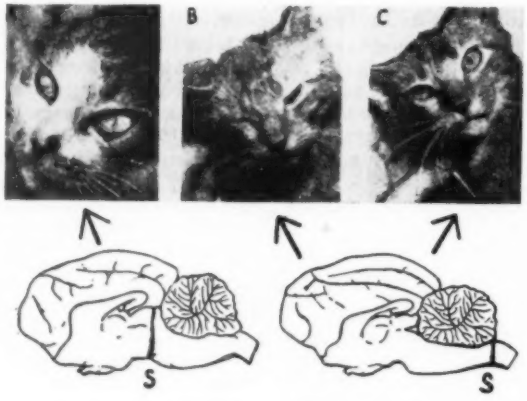

FIG. 4.—Cerveau isolé and encéphale isolé preparation of the cat. (From Bremer, 1935.)

although both the olfactory and the optic nerve have remained connected with the upper part of the brain. And if leads are taken off from the cortex the record shows the typical high-voltage slow-wave sleep-pattern. Some preparations were kept alive for days, and the cat's head was asleep all the time.

In the encéphale isolé the section is made below the medulla oblongata, as illustrated on the right side of Fig. 4; all cranial nerves remain connected with the upper portion of the brain. The encéphale isolé preparation exhibits mainly periods of wakefulness which alternate with periods of sleep. The eyes are wide open, the nictitating membrane is withdrawn, the pupils are dilated, and their diameter changes from moment to moment. The eyes show small exploratory movements, and will follow an object, but if the object is quickly brought close to the eye the lids close. Sounds, particularly voices, produce ear movements, such as orientation of the ears towards the sound. But the cat exhibits no emotional reaction either of fear or of anger; it seems to be emotionally undisturbed. As Bremer expressed it, "l'animal donne l'impression de regarder paisiblement ce qui l'entoure." When the preparation is asleep the E.E.G. pattern of the encéphale isolé is that characteristic for sleep, but when it is woken up—for instance, by a noise—the slow high-voltage waves are at once broken up, desynchronized, and replaced by low-voltage fast activity.

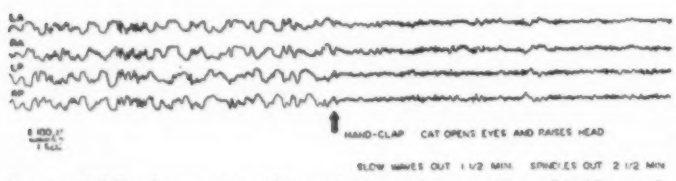

FIG. 3.—E.E.G. of a cat when asleep and when woken up. (From Lindsley *et al.*, 1950.)

These beautiful observations seemed to bear out the idea of Bremer that sleep is the result of deafferentation of the cortex, and yet, in anaesthesia, impulses from the periphery reach the cortex. When, in an anaesthetized cat or in a sleeping encéphale isolé, we stimulate an afferent nerve, a strong evoked response is produced in the sensory area of the cortex. In fact, the response is greater than that elicited during the waking state, as illustrated in Fig. 5 on a preparation in which the transection of the brain stem was made at a level between that of the cerveau and the encéphale isolé, in front of the medulla. Such a prebulbar preparation behaves like an encéphale isolé, but has the advantage of exhibiting a more stable sleep, from which it can be awakened. Fig. 5 shows records from the acoustic cortical area. D gives the size of the pupils which indicates whether the cat's head is asleep or awake.

The tracings 1 and 3 were taken while the preparation was asleep. We see, under A, the typical high-voltage slow-wave activity with a spindle burst at the end. At B a strong auditory-evoked response was elicited by an electric shock applied to the auditory pathway in the medial geniculate nucleus. C is the same as B, but taken on a slower time-base to show the after-discharge. There are always eight superimposed evoked responses. When the preparation has been aroused at 2 by blowing air into the nostrils, and when the record is activated and desynchronized—when the pupils are dilated and the eyes move about—the evoked response is much smaller.

Similar results are obtained in anaesthetized cats. The cortex thus receives the signals in anaesthesia as they travel up the ascending pathways. Bremer's results and his concept of deafferentation of the cortex thus requires some additional interpretation. This has been provided by Moruzzi and Magoun (1949) in their classical paper on "The brain stem reticular formation and activation of the E.E.G."

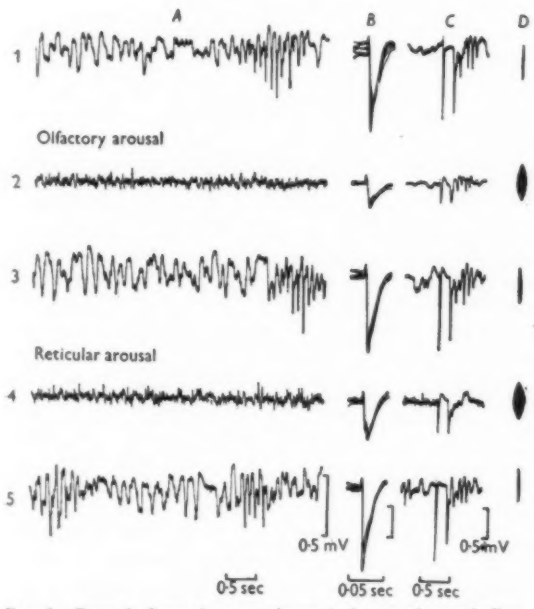

Fig. 5.—Records from the acoustic cortical area of a prebulbar preparation of the cat. B and C, superimposed impulses. D, size of pupil. At 1, 3, and 5, preparation "asleep"; at 2, aroused by blowing air into the nostrils, and at 4 by electrical stimulation of the reticular formation. (From Desmedt and La Grutta, 1957.)

The Reticular Activating System

In the central core of the brain stem from the medulla through the tegmentum of the mesencephalon to the diencephalon, to the epithalamus, subthalamus, and thalamus, we find diffuse aggregations of cells of different types and sizes, separated by a wealth of fibres travelling in all directions; the reticular formation. This diffuse system in the middle of the brain stem exerts an activating influence on the cortex, and it receives sensory signals from collaterals of all kinds of ascending fibres,

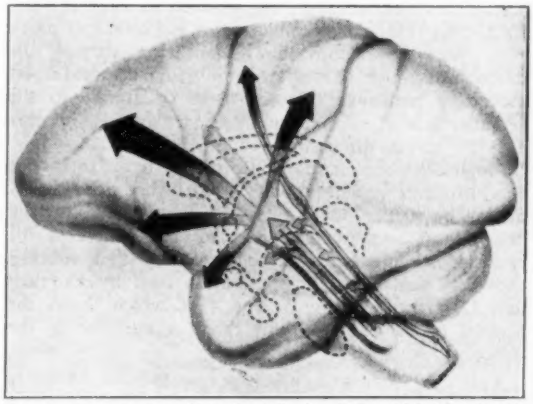

Fig. 6.—Lateral view of monkey's brain within which is projected the classical somatic afferent pathway to the sensory cortex and the ascending reticular system in the central brain stem, receiving afferent collaterals and projecting diffusely to the cortex. (From Magoun, 1954.)

from the somato-sensory fibres in the medial lemnisci, from the auditory fibres in the lateral lemnisci, from the other cranial nerves, and from visceral afferent fibres. An ascending fibre which passes along the classical pathway direct to a specific area in the cortex via its relay nuclei, gives off collaterals to the reticular formation, which then in turn sends impulses to practically the whole cortex, desynchronizing its high-voltage slow-wave activity and activating or alerting the cortex. This arrangement is illustrated in Figs. 6 and 7.

Fig. 6 is a lateral view of the monkey's brain within which is projected the classical somatic afferent path to the sensory cortex and the ascending reticular system, receiving afferent collaterals and projecting diffusely to the cortex. In Fig. 7 the classical

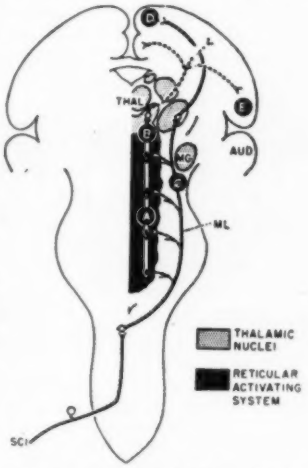

Fig. 7.—Diagram of brain showing classical somatic afferent pathway to sensory cortex (solid line) and ascending reticular system (black) with its diffuse cortical projections. (From French, Verzeano, and Magoun, 1953.)

somatic afferent pathway is represented by the solid line. It starts from the sciatic nerve, passes the nucleus gracilis, then via the medial lemniscus and the thalamic relay nucleus to the sensory cortex. The dotted lines represent the ascending reticular system with its diffuse cortical projection.

The conduction time of an impulse travelling via the classical ascending pathway reached the cortex at D in 11 msec., but, travelling to E via the reticular formation with its numerous synaptic relays, it took 54 msec., from the sciatic to A, 13 m.sec., and from A to B, 41 m.sec.

When we arouse, alert, or awaken a "sleeping" cortex by an afferent stimulus, say, by stimulation of the sciatic nerve or, as in the experiments of Desmedt and La Grutta (1957), by stimulation of the olfactory nerve —air was blown into the nostrils—the arousal, the desynchronization, is mediated not via the classical direct ascending pathways but via these collaterals to the reticular formation. We can arouse a "sleeping" cortex also by direct stimulation of the reticular formation through electrodes inserted into this system. In fact, it was Moruzzi and Magoun (1949) who first clearly demonstrated that the E.E.G. in a lightly anaesthetized animal can be desynchronized by stimulation of the reticular formation in the brain stem. This effect is shown in the prebulbar preparation used by Desmedt and La Grutta in Fig. 5, line 4 of which shows the arousal of the cat's head by direct stimulation of the reticular formation.

This kind of technique is now widely used. Bradley and Key (1958) used it to find out if a drug which prevents arousal does so by acting on these collaterals or on the reticular formation itself. If the drug acts on the collaterals it will prevent arousal from afferent stimulation, but without affecting the classical ascending pathways, and without preventing the arousal on direct stimulation of the reticular formation. If it acts on the system itself, direct stimulation of the system will also be ineffective.

The present concept of the reticular formation regards this structure as a unit which is activated as a whole. This concept has been extremely fruitful, and has greatly advanced our knowledge of the physiological function of the structures located in the central core of the brain stem. However, it is necessary to point out that the reticular formation consists of numerous anatomically discrete nuclei, as shown by Olszewski (1954), by Olszewski and Baxter (1954), and by Brodal (1957). Each of these nuclei may subserve distinct functions, and their final elucidation may entail changes in our present concept of the reticular formation—as happened with the views originally held on the function of the hypothalamus.

At present, however, we are justified in stating that arousal, wakefulness, or the conscious state can be expressed in physiological terms as a function of the ascending reticular formation in alerting the cortex. In the primitive simile I used at the beginning of the lecture, the switching on of the light to illuminate the room would correspond to the alerting function of the ascending reticular system. Bremer's concept that sleep is a functional deafferentation of the cerebrum is essentially true, though not in the sense originally envisaged. At that time only the classical ascending paths to the cortex were known. It is not interruption of these pathways, but functional deafferentation from the medial portion of the brain stem, or elimination of the waking influence of the ascending reticular activating system, which explains his results. This has been confirmed by placing lesions within the area of the ascending reticular formation.

Lesions in the Reticular Activating System

When Lindsley, Bowden, and Magoun (1949) performed their first experiments of this kind, they in a way changed the behaviour of a waking encéphale isolé of the cat into that of the permanently sleeping cerveau isolé by discrete lesions placed within the area of the ascending reticular formation. Lesions outside this area did not produce this behavioural change.

Later, Lindsley *et al.* (1950) obtained similar results in chronic experiments. Fig. 8 is taken from their paper. At A is shown a cat which is awake and standing, and the E.E.G. gives the characteristic awake pattern. This

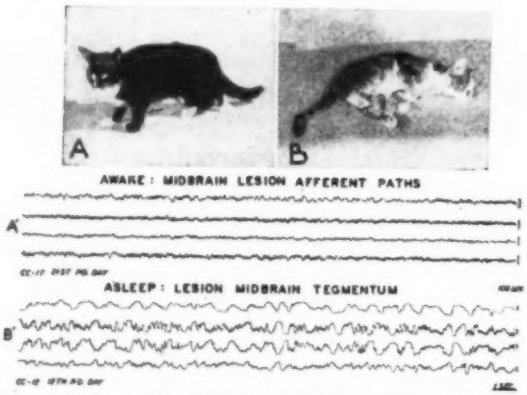

FIG. 8.—Effect on behaviour and E.E.G. of a chronic lesion in the lateral parts of the mid-brain interrupting the ascending sensory pathways (A and A') and of a chronic lesion in the central part of the tegmentum (B and B'). (From Lindsley *et al.*, 1950.)

cat has a chronic lesion in the lateral parts of the mid-brain interrupting the sensory paths but sparing the central core. B shows a cat lying asleep and giving the characteristic sleeping E.E.G. This cat has a chronic lesion in the central part of the tegmentum, sparing the sensory pathways.

Similar chronic somnolence with electroencephalographic synchrony was obtained with diencephalic lesions bordering the third ventricle. In Fig. 9, from the same paper, paramedian lesions which produced such somnolence are projected into the mid-sagittal-plane of the brain stem. A is a tegmental, B a subthalamic, and C a subthalamic-thalamic lesion. These cats, when undisturbed, lay motionless on their sides, somnolent or asleep. At the beginning they could not be aroused, but after days or weeks, according to the site of the lesion, an afferent stimulus—for instance, a buzzer—would arouse them for a moment, as shown by desynchronization of the E.E.G. This activation differed from normal arousal in that it terminated almost immediately upon the cessation of the arousing stimulus.

Lesions in the lower part of the reticular formation did not produce the sleep-like condition. The cat with the lesion D remained awake. The more rostral lesion of the peri-aqueductal grey matter (E) which invaded the caudal part of the thalamus produced somnolence and synchronization of the E.E.G. for about a week; later the cat became progressively more wakeful.

Lesions in the rostral part of the activating system of the monkeys appeared to affect the behaviour and electrocortical activity of the animal even more drastically than in cats. Fig. 10 shows midsagittal reconstructions of brain-stem lesions which rendered the monkeys totally and permanently helpless and produced synchronous E.E.G.s incapable of activation. French and Magoun (1952) describe the condition in the monkeys as one simulating coma, or at least stupor, in man. And "as in such states in man, these animals would occasionally respond briefly to intense stimuli by reflex withdrawal of extremities or by diffuse inappropriate movement, at which time the eyes would open in a superficial semblance of wakefulness; but at no time was there any suggestion that the animal was alertly responsive to the stimuli or to his surroundings."

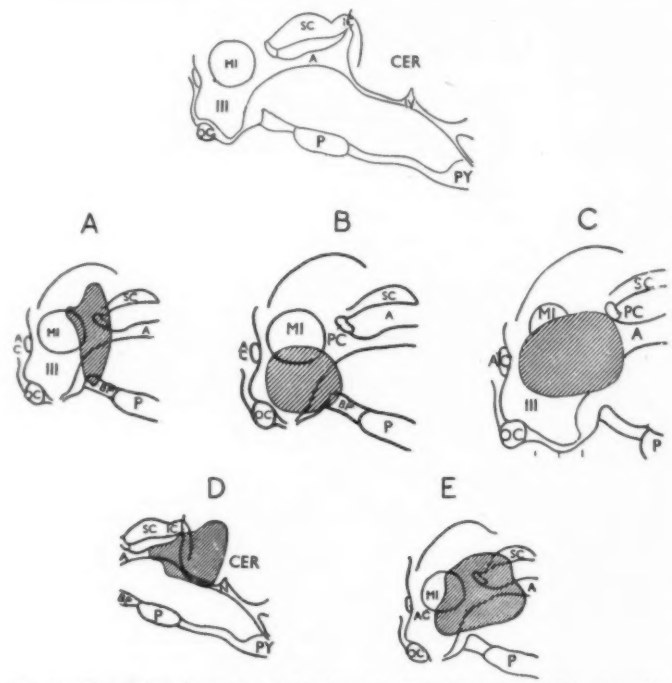

FIG. 9.—Paramedian brain-stem lesions in cats (A to E) projected into the mid-sagittal plane of the brain stem. Upper diagram: mid-sagittal plane of cat's brain for orientation. A=aqueduct; CER=cerebellum; IC and SC=inferior and superior colliculi; MI=massa intermedia; P=pons; Py=pyramidal crossing; III and IV=third and fourth ventricles. For details of the lesions and the behavioural changes they produce, see text. (From Lindsley *et al.*, 1950.)

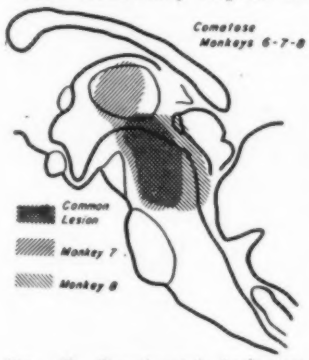

FIG. 10.—Experimental brain-stem lesions in three monkeys which produced a state simulating coma or stupor in man and a synchronous E.E.G. which could not be activated. Lesions projected into the mid-sagittal plane of the brain stem. (From French and Magoun, 1952.)

After having given in the mid-saggital plane reconstructions of the lesions which in cats and monkeys produce a state of somnolence, I want to return to Fig. 2, and, although the area given by Jefferson is a little more extensive, the similarity is striking, and I think many of the clinical cases of loss of consciousness reviewed at the beginning of the lecture can safely be expressed in physiological terms as an interference with the ascending reticular activating system.

An analysis of neurological cases involving loss of consciousness must start with a search for changes in this part of the brain stem. Take, for example, the stupor of concussion: Foltz and Schmidt (1956) compared the evoked potentials on stimulation of the sciatic nerve in the reticular formation with that in the classical sensory path of the medial lemniscus after an accelerating blow on the monkey's head. "The responses in the reticular formation were selectively, uniformly, and dramatically absent after a sufficient blow on the head," whereas the responses in the lemniscus remained unchanged. This is shown in Fig. 11.

Sleep Produced by Excitation of Certain Brain-stem Areas

There is an observation by Hess (1944, 1954) which at first sight does not seem to conform with the general picture given of the mechanisms responsible for sleep and wakefulness. Hess found that cats curled up and went to sleep in a wholly normal manner when he stimulated certain medially situated brain-stem areas in the diencephalon—the massa intermedia or the intralaminar thalamic nuclei—through implanted electrodes, but only—and this is important—when stimulation was with low frequency and low voltage. The E.E.G. showed the typical slow high-voltage wave pattern as shown by Hess, Koella, and Akert (1953).

To understand this observation we must go back to an old observation by Dempsey and Morrison (1942), usually called the "recruiting response of the diffuse thalamo-cortical system"; and to explain it I shall make use of a diagram (Fig. 12) from Bradley (1958). It shows the general arrangement of the diffuse thalamic projection system and the reticular activating system. Dempsey and Morison stimulated, in cats under

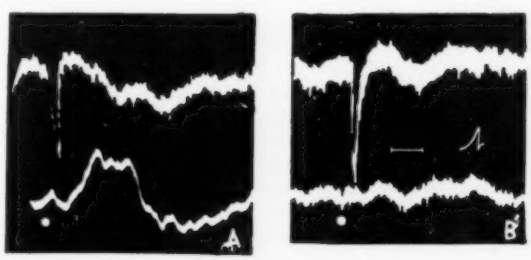

FIG. 11.—Oscilloscope record of concomitant evoked potentials in brain-stem reticular formation (lower trace) and medial lemniscus (upper trace). At A, control without concussion; at B, after acceleration concussion produced by a blow against the monkey's head. (From Foltz and Schmidt, 1956.)

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pentobarbitone sodium ("nembutal") anaesthesia, these medially situated thalamic nuclei, which are not the relay stations for the specific projection system to localized areas of the cortex—these, as shown in Fig. 12, are the lateral nuclei. The medial nuclei project diffusely to the cortex, like the reticular activating system; they are, in fact, sometimes included in this system. When Dempsey and Morison stimulated this region, but only with low frequencies, 8-12/sec., they

FIG. 12.—Diagrammatic representation of the reticular formation and the diffuse thalamic projection system. (From Bradley, 1958.)

recorded from the whole cortex high-voltage slow waves, one for each shock. At the beginning of stimulation these waves increased in amplitude; they recruited to a maximum: therefore the term "recruiting response." According to Dempsey and Morison, the recruiting response is identical with the spontaneous bursts of high-voltage 8-10/sec. activity which are so characteristic of deep pentobarbitone sodium anaesthesia.

It is interesting that we can drive the cortex in this rhythm on stimulation from the medial thalamic nuclei provided we use weak current and a rate of stimulation close to that of the normal slow rhythm of the sleeping brain.

Hess probably stimulated this diffuse thalamic projection system, producing something akin to the recruiting response. Hess also used a stimulation rate of 8/sec.

Hess's sleeping cats were easily aroused, for instance, by the smell of meat, and this is in accord with the finding by Moruzzi and Magoun that in the encéphale isolé the recruiting response is abolished by sensory stimulation, such as loud whistling, blowing on the head or eyes, or rubbing the nose, or by direct stimulation of the bulbar reticular formation.

Thus stimulation in this region, with low voltage and low frequencies, resulted in the recruiting response of Dempsey and Morison and led to sleep in the experiments of Hess. And stimulation of the reticular activating system, directly or indirectly through collaterals from the ascending paths, abolished the recruiting response and led to arousal.

Reticular Formation and Anaesthesia

There is now this question: Is the unconsciousness of anaesthesia the result of reversible reduction of activity in this region? Have anaesthetics, even if they act diffusely upon the brain, a predilection for the reticular activating system; and does block of the ascending conduction in this medially situated system of the brain stem provide a neural basis for the anaesthetic state?

These questions have been asked by French, Verzeano, and Magoun (1953), and by the Arduinis (1954), and have been answered in the affirmative. These authors have convincingly shown that anaesthetics block impulses propagated over the medial pathways of the brain stem to the cortex, but that the laterally conducted impulses remain unimpaired and reach the cortex. Fig. 13 shows in a monkey evoked responses to an auditory stimulus recorded from the reticular formation and from the lateral direct ascending pathway to the cortex—that is, from the lateral lemniscus. The evoked response in the reticular formation is abolished after one minute of ether anaesthesia; the response in the lateral lemniscus remains unimpaired even after eight minutes of ether anaesthesia.

The susceptibility of the brain-stem reticular formation to anaesthetics is not surprising once we realize that anaesthetics are apparently able to block transmission across a synapse much more readily than conduction along a nerve fibre (Larrabee and Posternak, 1952), and that the reticular formation is characterized by its multineural or multisynaptic organization, so that impulses have to pass one synapse after another, in contrast to the few encountered by an impulse ascending to the lateral pathway.

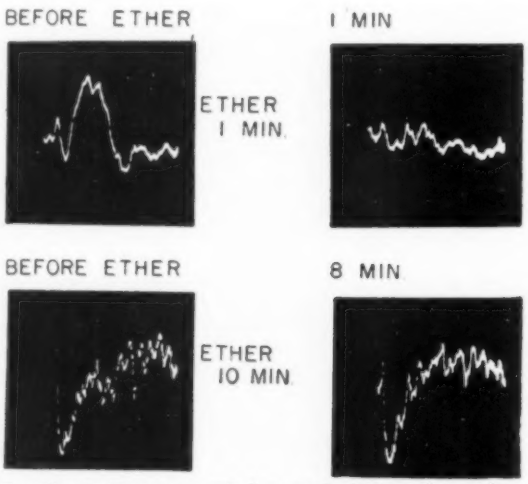

FIG. 13.—Oscilloscope records from the brain stem of a monkey. Effect of ether on evoked auditory responses in the reticular formation (upper records) and in the lateral lemniscus (lower records). (From French *et al.*, 1953.)

Anaesthesia-like Conditions Produced by Injections of Drugs into the Cerebral Ventricles of Unanaesthetized Animals

The structures which on excitation cause arousal and on injury loss of wakefulness and which apparently are selectively blocked in anaesthesia are situated close to the midline, lining the walls of the third ventricle and of the upper end of the aqueduct. If the loss of consciousness in anaesthesia is the result of a selective action on these structures, should it then not be possible to produce the anaesthetic state by injecting anaesthetics into the cerebral cavities? Such injections I have made, but I have to confess *not* as the result of such logical considerations as they should have been. What happened was as follows.

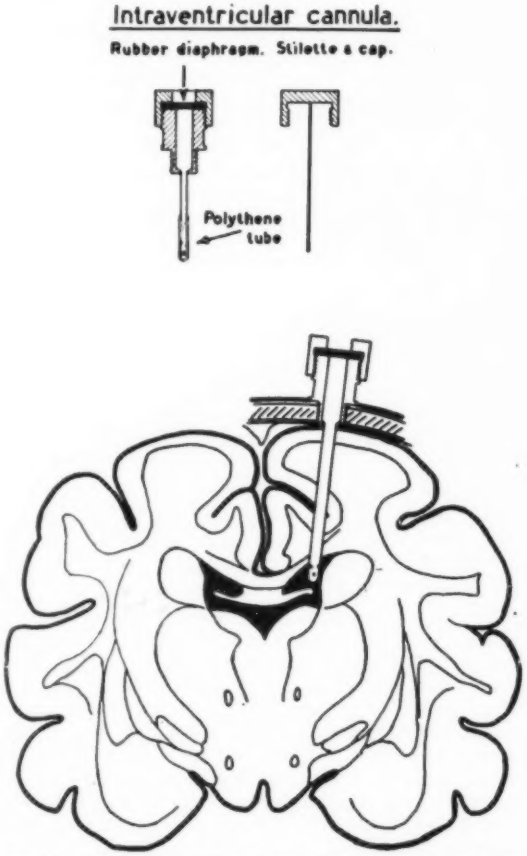

FIG. 14.—Diagram illustrating method of injecting substances into the lateral ventricle of the cat's brain through a Collison cannula screwed into the skull. (From Feldberg and Sherwood, 1953.)

About five years ago, Dr. Sherwood and I started experiments in which we injected drugs into the cerebral ventricular system of the cat. A cannula was permanently implanted into the skull with its tip lying in the lateral ventricle. A diagram of the implanted cannula is shown in Fig. 14. Injections could be made through the rubber diaphragm in the unanaesthetized cat without the animal being aware of it.

Amongst the various drugs and ions we injected, we found three which produced anaesthesia or sleep-like conditions (Feldberg and Sherwood, 1954, 1957). They were adrenaline, noradrenaline, and $CaCl_2$. An anaesthetic or soporific effect of these three substances had been observed before (Bass, 1914; Marinesco, Sarger, and Kreindler, 1929; Leimdorfer and Metzner, 1949; Leimdorfer, 1950). Fig. 15 is from a film we took and shows the condition produced in a cat about half an hour after an intraventricular injection of 50 μg. of adrenaline. The animal could be turned on its back or lifted by its front or hind legs without it struggling. The eyes were closed most of the time, but when disturbed the cat stared with open, apparently unseeing, eyes. It reacted slowly, if at all, when pricked with a pin. The condition resembled that of light anaesthesia.

Adrenaline, noradrenaline, and $CaCl_2$ are neither anaesthetics nor hypnotics. This made me wonder what would happen if the latter were injected intraventricularly. Would they also produce an anaesthesia-like condition?

I tried barbiturates, urethane, $MgCl_2$, chloral, and chloralose (Feldberg, 1958). With the exception of chloral, they are all used as anaesthetics in animal experiments. But the amounts I injected intraventricularly were so small—a few milligrams or less—that they would not have affected wakefulness if given intravenously.

Unfortunately, the barbiturates proved unsuitable because they are soluble in strong alkali only, and I did not want to inject strong alkaline solutions into the brain cavities. However, I could dissolve at a *p*H of about 8 very small amounts, and when injected intraventricularly they often, though not always, produced sleep or an anaesthesia-like condition. Urethane produced only sleep, not anaesthesia. The cats could always be aroused, but when they were then left undisturbed they curled up again and went to sleep. On the other hand, intraventricular injections of a few milligrams of $MgCl_2$, chloral, or chloralose produced anaesthesia-like conditions which lasted for one to three hours.

The first effect produced by all these substances was hyperphagia accompanied or followed by ataxia. The effect occurred even with doses too small to produce sleep or anaesthesia—for instance, 0.2 mg. of chloralose

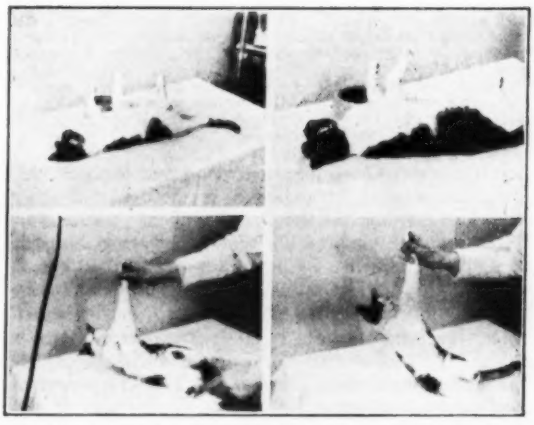

FIG. 15.—Anaesthesia-like condition in a cat produced by 50 μg. of adrenaline injected into the lateral cerebral ventricle. About half an hour after the injection. (From a film made by Feldberg and Sherwood, 1959.)

was sufficient, and after the larger doses it happened again when the cats came round from their sleep or anaesthesia. It was always a striking picture.

Immediately after the injection, when placed in its cage, the cat would rush to the meat-pot, swaying and stumbling, if already ataxic, and then, unable to stand or sit, would lie on its belly, and with its head shaking or rocking would voraciously devour the whole pot of meat, or even more. Sometimes, while still eating, the cat would be overcome by anaesthesia, and the head would just drop into the meat-pot or on to its rim. I remember that one cat, immediately after the intraventricular injection of 2 mg. of chloralose, crawled to the meat-pot and just had time to put its head into it before falling asleep.

If the cats were offered both meat and milk, they usually went for the meat; several cats, however, preferred milk. In a few cats there was compulsive biting and gnawing of inedible objects—a proffered pencil, a piece of wood lying in the cage, or, less appreciated, electrode leads attached to the cat.

In rats and cats, small bilateral electrolytic lesions close to the wall of the hypothalamus lead to hyperphagia and obesity (Hetherington, 1941; Anand and Brobeck, 1951a, 1951b). On the other hand, lesions placed more laterally in the hypothalamus completely inhibit the food intake, so that the animals would die of starvation if not fed by tube. The lateral lesions abolish also the hyperphagia produced by the more medially placed lesions. Fig. 16 illustrates the sites of such lesions in

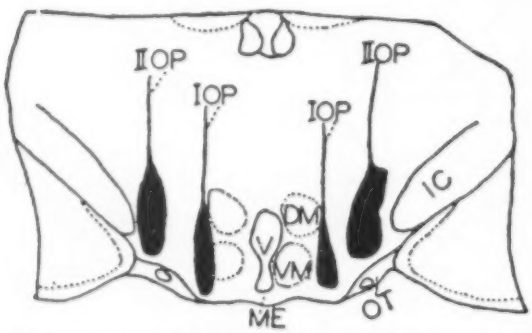

FIG. 16.—Diagram of a cross-section of a rat's brain stem. The black areas represent bilateral lesions in the hypothalamus; the dorsal prolongations represent electrode tracts. The medial lesions (I OP) induced hyperphagia and obesity. Feeding disappeared after the production of the lateral lesions (II OP). DM and VM = nucleus hypothalamicus dorso- and ventromedialis; V = third ventricle; ME = median eminence; OT = optic tract; IC = internal capsule. (From Anand and Brobeck, 1951b.)

the rat's brain. According to Anand and Brobeck, the lateral areas must be regarded as the actual feeding centres responsible for the central hunger reaction and the urge to eat, whereas the ventro-medial nuclei exert an inhibitory influence on these feeding centres. Bilateral lesions between the two areas also remove the inhibitory control and produce hyperphagia.

The anaesthetics when injected intraventricularly impinge on these medially situated nuclei, and, by "anaesthetizing" them, remove the inhibitory control over the feeding centre, thus producing the urge to eat.

Hyperphagia can apparently also occur when the anaesthetics reach the brain via the blood-stream, provided that anaesthesia does not supervene too quickly. At least, I found this so with chloralose. To produce full anaesthesia in a cat one usually injects 70 to 90 mg./kg. intravenously. When I injected intravenously only 10 mg./kg., the cats began to eat immediately after the injection, although they had been well fed before, and continued to eat vigorously and without interruption for 10 to 20 minutes and then drank milk or water for another few minutes. While eating and drinking they became very ataxic.

To come back, however, to the anaesthesia-like condition. When deeply under, the cat can be turned on its side or back, and it remains in this position. The nictitating membranes are relaxed, the pupils are narrow and slit-like, the eyes are mostly closed. The respiration is slow, sometimes very slow, and the heart rate shows strong sinus arrhythmia which is characteristic for sleep. In addition, each substance may produce specific effects which are also seen when the substance is given by the intravenous route. For instance, a characteristic feature of intravenous chloralose anaesthesia is the hyperexcitability. When a cat is under chloralose anaesthesia, tapping its foot causes a strong twitch of the leg, and a sudden noise or banging at the operating-table may result in vigorous jerking. The same hyperexcitability is found after intraventricular chloralose. This suggests that it is due to a subcortical action of chloralose, at structures close to the wall of the ventricles or aqueduct. One thinks of the descending reticular formation. The hyperexcitability is actually so strong and persistent after intraventricular chloralose that it would be difficult to perform operations in this condition.

And, finally, what about the E.E.G.? Would we record the typical synchronization so characteristic for sleep and anaesthesia; the high-voltage slow waves, the spindle bursts?

For some other purpose Professor Malcolm (1958), together with Mr. Gold, had developed a beautiful little radio-transmitter which a cat can carry on its back without apparent discomfort. Fig. 17 shows this transmitter strapped on to a cat. The cat had a burr-hole made in the skull so that a microelectrode could be lowered into the superficial layers of the cortex; the electrode was connected to the transmitter, and the E.E.G. could be picked up in another room and photographed. For our purpose, the cat also had an implanted cannula for intraventricular injections.

Fig. 18 shows the result of an experiment by Professor Malcolm and myself. A shows the noise level of the

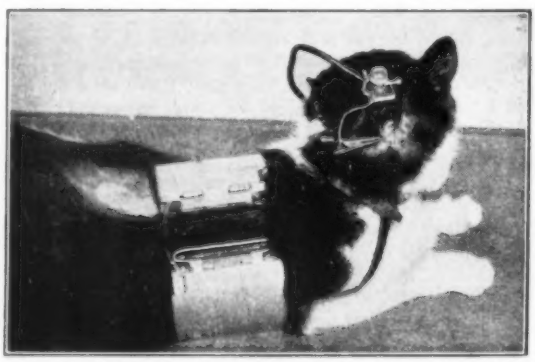

FIG. 17.—Radio-transmitter strapped on to a cat. (From Malcolm, 1958.)

transmitter when not connected to the electrode. B shows the fully desynchronized E.E.G. of the waking cat. Then 2.4 mg. of chloralose was injected intraventricularly. C and D were taken 10 and 20 minutes, E and F 40 minutes, and G 70 minutes after the injection, while the cat was still deeply under and could not be

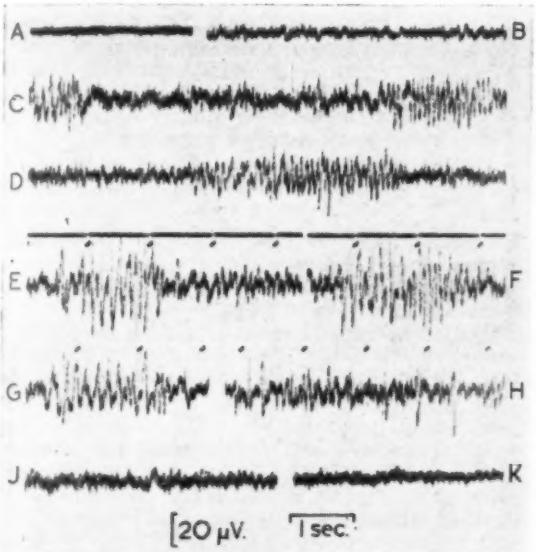

Fig. 18.—Records taken from a microelectrode in the superficial layer of the cerebral cortex of a cat with the radio-transmitter shown in Fig. 17. A, noise level; B, E.E.G. before, and C to K at various times after, an injection of 2.4 mg. of chloralose into the lateral cerebral ventricle of a 3-kg. cat. For details see text. (From Feldberg and Malcolm, 1959.)

roused to full wakefulness. The E.E.G. shows bursts of typical high-voltage waves. H and J were taken about two hours after the injection. Between H and J, I went into the room where the cat was lying and succeeded in arousing it. She stretched out her forelegs like a cat waking up, and Professor Malcolm at once noted a strong reduction of the E.E.G. activity. The E.E.G. became desynchronized as shown at J. K was taken nearly four hours after the injection. The cat was awake. The E.E.G. fully desynchronized. This record was taken during the stage where the ventromedial nuclei of the hypothalamus were apparently still "anaesthetized" because it was taken while the cat lapped up a full pot of milk.

With this experiment I have come to the end of my attempt to present a physiological approach to the problem of consciousness, or unconsciousness, and of the neural basis of the anaesthetic state. I have tried to show how this problem has developed over the past 25 years, and how essential it has been for this development that the clinician, the physiologist, the pharmacologist, and the anatomist have shared their experience.

Summary

It is not so long ago since neurologists supposed that consciousness was exclusively a function of the cerebral cortex, and that the loss of consciousness from cerebral haemorrhage was caused by general cerebral anaemia. Yet removal of the cerebral hemispheres does not lead to loss of consciousness but to a condition of idiocy. And there is abundant clinical evidence that disturbances of consciousness are associated not with lesions of the cerebral cortex but with lesions of the diencephalon and perhaps of the rostral parts of the mesencephalon. These findings are in accord with the conclusions arrived at by the physiologist.

Bremer started from the hypothesis that sleep is the result of deafferentation—that is, of suppression of the impulses which usually reach the cerebral cortex. He showed in cats that after transverse section of the brain at mid-collicular level the head of such a cerveau isolé behaved as if it were asleep, and its E.E.G. showed the typical high-voltage slow-wave pattern. However, the cerebral cortex receives the signals in anaesthesia as they travel up the ascending pathways. Bremer's concept of deafferentation thus required additional interpretation.

This interpretation was provided by the work of Magoun and Moruzzi on the reticular activating system of the brain stem. This system of diffuse aggregation of cells in the central core of the brain stem receives sensory signals from collaterals of all kinds of ascending fibres and sends impulses to practically the whole cortex, desynchronizing its high-voltage slow-wave E.E.G. pattern and alerting the cortex. Arousal, wakefulness, or the conscious state can be expressed in physiological terms as a function of the ascending reticular formation in alerting the cortex.

Lesions in the area of the ascending reticular formation produce sleep-like conditions.

During the stupor of concussion the normal responses to an afferent stimulus in the reticular formation are absent, but those in the lateral ascending pathways remain.

Anaesthetics, even if they act diffusely upon the brain, have a predilection for the reticular activating system: they block the ascending conduction in this medially situated system of the brain stem, whereas the laterally conducted impulses remain unimpaired and reach the cortex.

At first sight the classical observation of Hess that a cat falls asleep on weak low-frequency stimulation of the massa intermedia or the medially situated intralaminar thalamic nuclei does not seem to conform with these findings. Hess's effect appears to be related to the recruiting response of the diffuse thalamo-cortical system. Both effects suggest that we can drive the cortex on stimulation of the medial thalamic nuclei provided we use weak current and a rate of stimulation close to that of the normal slow rhythm of the sleeping brain.

Since the structures which on excitation cause arousal, and on injury loss of wakefulness, and which are selectively blocked in anaesthesia are situated close to the midline lining the walls of the third ventricle and of the aqueduct, it is not surprising that sleep-like and anaesthesia-like conditions are produced with drugs injected into the lateral ventricle. Such effects were produced with adrenaline, noradrenaline, and $CaCl_2$, and also with some anaesthetics ($MgCl_2$, urethane, chloral, and chloralose) injected in amounts far too small to produce such effects on intravenous injection. The immediate effect of the anaesthetics was hyperphagia, probably due to "anaesthesia" of the ventro-medial nuclei of the hypothalamus, which are known to exert an inhibitory influence on the more laterally situated feeding centres.

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According to a British United Press report from Frankfurt, 428 surgeons, 125 dentists, and 30 veterinary surgeons fled from Eastern Germany to the West in the first eight months of this year.

TREATMENT OF IRON DEFICIENCY WITH FERROUS FUMARATE

ASSESSMENT BY A STATISTICALLY ACCURATE METHOD

BY

H. T. SWAN, M.B., M.R.C.P., D.C.H.

Assistant Haematologist, Royal Infirmary and Royal Hospital, Sheffield

WITH STATISTICAL ASSISTANCE FROM

G. H. JOWETT, B.A., Ph.D.*

Senior Lecturer in Charge, Department of Statistics, University of Sheffield

It is desirable to know how the new iron preparation ferrous fumarate compares with pre-existing therapies. To commend itself for routine use it should be at least as effective as established drugs, and have fewer or no unpleasant side-effects, as well as being safe. The results reported below show that these requirements appear to be satisfied by ferrous fumarate.

For many years the mainstay of iron therapy has been ferrous sulphate. In 1836, Ashwell, when discussing the treatment of chlorosis, said that the sulphate of iron was "probably the most efficacious and possessed more specific properties than any of the rest." Davidson (1933) urged the use of ferrous sulphate tablets, adequate treatment with which still costs only one penny a week. Gastric symptoms such as epigastric discomfort, nausea, and vomiting have often been reported after its use. In a recent comparative trial the incidence of such side-effects was found to be 13% with ferrous sulphate (O'Sullivan, Higgins, and Wilkinson, 1955). Girdwood (1952) drew attention to a strong psychological intolerance shown by his patients towards tablets of ferrous sulphate, but only when they were coated green. Kerr and Davidson (1958) showed by a double blind trial, however, that unrecognized control pills caused the same incidence of side-effects as did the active iron pills, including ferrous sulphate. Ingestion of an overdose of ferrous sulphate by children who have mistaken the green sugar-coated tablets for sweets has resulted in death (Forbes, 1947; Thomson, 1947) and has been shown to cause pyloric stenosis and fibrous stricture of the pyloric antrum or mid-portion of the stomach (Ross, 1953; Shepherd, 1955). Despite these disadvantages, ferrous sulphate is still accepted as a very effective therapeutic compound.

Many alternative potent preparations of iron have been used in order to avoid undesirable side-effects and dangers to children. Ferrous gluconate, originally recommended by Reznikoff and Goebel (1937), has lately become one of the most popular of iron tablets. These tablets are sugar-coated and relatively cheap, although four times as expensive as ferrous sulphate. The incidence of toxic side-effects has been estimated at 4%, with clinical efficacy similar to that of ferrous sulphate (O'Sullivan *et al.*, 1955). Deaths attributable to overdosage had not been reported by 1955 (Hoppe, Marcelli, and Tainter) and no report of a death resulting from ferrous gluconate has been seen since then. There have been many other effective but even more expensive

*Now at Department of Statistics, University of Melbourne, Australia.

iron preparations on the market. It has yet to be proved that they are better than the established drugs.

Ferrous fumarate, an organic iron compound, is a new contestant in the field. It is dispensed as small light-brown 200-mg. tablets which do not resemble sweets. The iron contained in them is very stable, thus removing the need for sugar coating, and this permits rapid disintegration of the tablets when ingested. If a tablet of ferrous fumarate is sucked it leaves a very slightly unpleasant taste which classes it apart from sweets, but there is no metallic astringent sensation.

The accompanying Table shows the ferrous iron content of four salts and the standard tablets prepared from them, together with their relative costs. The prices quoted have been taken from price-lists supplied in autumn, 1958.

Iron Content and Costs of Four Iron Preparations

	Ferrous Iron (Approx. %)	Standard Tablet (mg.)	Ferrous Iron per Tablet, Approx. (mg.)	Cost of Treatment for One Week (21 Tablets) at Hospital Rates per 1,000 Tablets
Ferrous fumarate	33	200	65	5d.*
,, gluconate *B.P.*	12	300	37·5	4d.
Ferrous succinate	25	150	37·5	4½d.*
Exsiccated ferrous sulphate *B.P.*	30	200	60	1d.

* Exclusive of purchase tax 1½d.

The toxic effects of ferrous fumarate on laboratory animals have been studied by Berenbaum, Child, Davis, Sharpe, Tomich, and Chalmers (1959). Rabbits given large doses of ferrous sulphate tablets developed severe gastric necrosis and chemical hepatitis. Ferrous gluconate produced similar but less intense effects, whereas ferrous succinate and ferrous fumarate usually caused little or no inflammatory reaction. In cats, the dose of ferrous fumarate required to produce vomiting was three times greater than the equivalent doses of the other three iron preparations.

It is the purpose of this paper to describe the effects of giving ferrous fumarate tablets to 64 patients suffering from iron deficiency, and to measure, so far as is possible, the efficacy of the drug and its toxic effects in clinical use.

Material and Methods

Since June, 1957, 64 patients have been treated with ferrous fumarate, 200 mg. (one tablet), by mouth three times daily after food. Fifty-five of these patients were selected as the result of peripheral blood examinations made in the departments of haematology of the Royal Infirmary and the Royal Hospital, Sheffield, at the request of hospital consultants and family doctors. Where a blood examination showed anaemia of any degree with definite red-cell hypochromia and it was believed that the anaemia was of iron-deficiency type, permission was sought from the clinician in charge of the case to treat the patient. The study was deliberately not restricted to the 37 patients who had a simple iron-deficiency anaemia unassociated with blood loss and resulting from too little dietary iron. It included 18 others suffering from "complicated" iron deficiency, some having heavy menstrual loss or alimentary blood loss, the remainder having various diagnoses such as are found in any medical or surgical ward, the patients being unselected apart from the presence of iron deficiency. The initial mean corpuscular haemoglobin concentration (M.C.H.C.) was estimated in 46 of these patients and was below 32% in all (normal range 32–36%). No patient in the main group had received iron therapy during the preceding six months.

Capillary blood was examined at weekly or fortnightly intervals over eight weeks during treatment. The haemoglobin estimations were made as oxyhaemoglobin, using the M.R.C. grey wedge photometer and the films stained with Leishman's stain. Where the M.C.H.C. was estimated, venous blood was used. The patients were given the opportunity of discussing symptoms at each visit, although leading questions were reserved for the final visit. No patient having once been treated with ferrous fumarate has been excluded from this series on the grounds of failure to respond or toxic effects.

Six women, one of them pregnant and all of them iron-deficient, were given ferrous fumarate as a severe test of its freedom from side-effects, because they had proved themselves to be intolerant to all the other iron preparations they had been given. Four patients suffering from post-gastrectomy iron-deficiency anaemia are discussed as a separate group.

Results

In the main group of 55 patients, the haemoglobin levels of the first 47 on treatment have been analysed statistically. The records for the remainder became available after this had been carried out, but the figures are consistent in every way with those included in the analysis.

Two pieces of statistical analysis were carried out on these data, and are reported here. The aim of the first of these was to study the mode of return of the haemoglobin levels to normal under treatment so as to obtain a rational criterion of success. The second has been concerned with the evaluation of the trial of ferrous fumarate in terms of this criterion, obtaining a figure of known statistical accuracy with which other workers may compare their own results using ferrous fumarate or any other iron preparation.

Analysis 1

In Fig. 1 is shown an example of the relationship between the haemoglobin level after a fixed number (k) of weeks on therapy and the initial haemoglobin level (in Fig. 1, k=2).

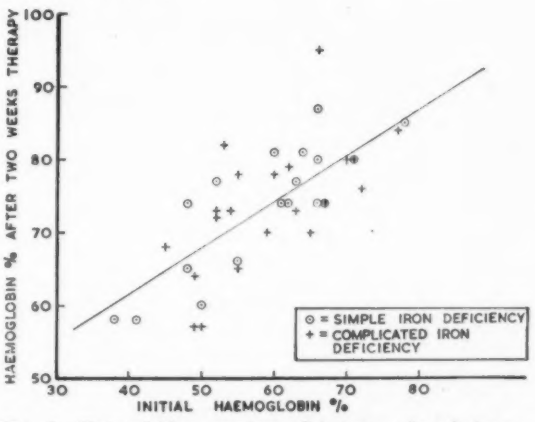

FIG. 1.—Haemoglobin percentage after two weeks of therapy related to initial haemoglobin.

Each point plotted corresponds to a particular patient, the total number of points being fewer than 47 because some patients did not appear for examination at the end of the appropriate week. A line of regression has been fitted, and may be taken as giving the relationship between the *mean* haemoglobin after k weeks and the initial haemoglobin. The two symbols used for the plotted points are for the different categories of patient, simple iron deficiencies being kept distinct from the complicated cases. There was no evidence (either prima facie or revealed by statistical significance tests) of any differences in the relationship for these two categories. A similar analysis was carried out for each week in therapy up to the eighth—that is, k=1 to 8—and it was observed that the regression line became higher and flatter as time went on, indicating the gradual return to normality. After a critical statistical examination of these trends it was found to be justifiable to summarize the return of haemoglobin to normal by means of a family of curves, shown in Fig. 2, which show the mean pattern of return to normal for patients starting treatment from different levels of haemoglobin.

Fig. 2 demonstrates clearly how markedly the effect of initial differences in haemoglobin level influences the rate of response during the first few weeks of therapy, the more anaemic groups responding more rapidly. The difference between the groups lessens with time and effectively dies out by the seventh week. The observations suggest that the haemoglobin level is still climbing slightly at the end of the eighth week, but it seems unlikely that any serious error will be committed by accepting the eight-week figure as effectively normal. Observations of the haemoglobin levels of individual patients deviate randomly from the appropriate value given by Fig. 2, with a standard deviation of 6.6.

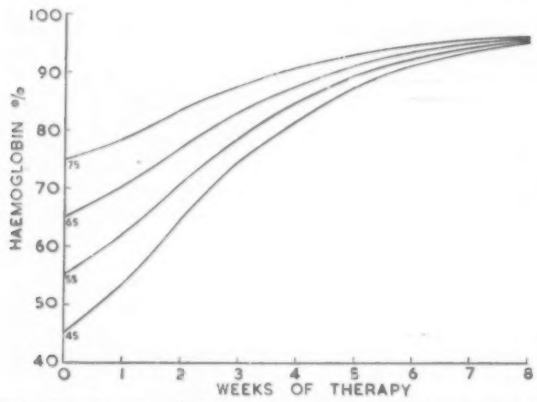

FIG. 2.—Mean haemoglobin percentage at successive stages of therapy for different initial haemoglobin levels. (100% Hb= 14.8 g./100 ml.).

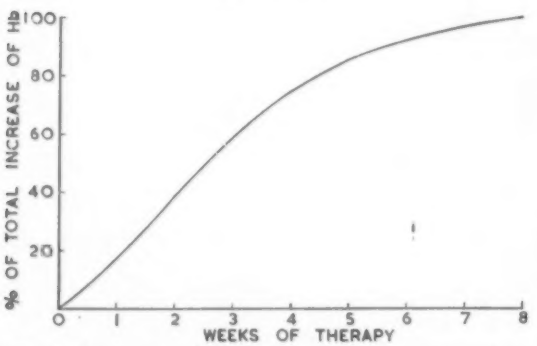

FIG. 3.—Recovery attained at successive weeks, expressed as percentage of increase of Hb achieved by eight weeks.

The pattern of return to normal does in fact admit a more concise representation than Fig. 2. If each of the curves of Fig. 2 is re-scaled so as to increase from 0 initially to 100 at eight weeks, the result is the single curve, applicable to all initial haemoglobin levels, shown in Fig. 3.

That all curves re-scale *exactly* into this curve is of course a consequence of the statistical method of fitting, but an alternative method of fitting which is described in the statistical appendix and which does not beg this important question leads to curves which differ only very slightly and do not give a superior fit to the data.

Analysis 2

In the light of Analysis 1, it was decided to summarize the effect of treatment on the haemoglobin level of individual patients by expressing, as a percentage, the ratio of the correction achieved by the end of the third week to that achieved by the end of the eighth week;

$$p \equiv \frac{x_3 - x_0}{x_8 - x_0} \times 100$$

where x_0 symbolizes the initial haemoglobin value, and x_3 and x_8 the measurements at the end of the third and eighth weeks of treatment respectively (see Statistical Appendix).

For the 53 available cases, the mean value of p—that is, the mean percentage recovery achieved by the end of the third week—was 59.0%; the standard deviation of p was 17.3, implying a variation from this figure of as much as $\pm$ 34.6 for individual cases, and implying a statistical accuracy for the mean of $\pm$4.8 (based on an estimated standard error of 2.4).

Response of Particular Patients to Ferrous Fumarate

1. Side-effects Caused by Ferrous Fumarate

Although each patient was repeatedly given the opportunity of commenting on the tablets, only 2 of the 55 patients in the main series made any adverse comment, remarking on slight epigastric discomfort which began 10 minutes after taking the tablets and lasted about two hours. Such discomfort was felt only during the first 10 days of therapy and disappeared entirely during continued treatment. Five patients considered constipation to be attributable to the tablets.

Amongst the nine others treated with ferrous fumarate but not as part of the main series, one suffered undesirable side-effects. She had been given ferrous fumarate because of her intolerance of other iron preparations, and is described in subsections 2 and 3 below.

2. Patients Intolerant of Other Iron Preparations

Two of the patients in the main series who remained symptom-free when taking ferrous fumarate had customarily felt sick with ferrous gluconate, and a third had vomited with ferrous sulphate. Outside the main series, six women were given ferrous fumarate on account of their intolerance of other iron preparations.

The *first*, aged 47, with simple iron deficiency, was becoming more anaemic in spite of two or three drops of colloidal iron which she took with food three times a day.

Even such small amounts caused slight nausea, but ferrous sulphate and ferrous gluconate caused vomiting and could not be tolerated at all. The *second*, aged 32, had been able to take an expensive chelated iron preparation during pregnancy, but not ferrous sulphate or ferrous gluconate. The *third*, aged 38, with menorrhagia, had been so intolerant of ferrous sulphate and ferrous gluconate by mouth that she had required two courses of intravenous iron in recent years. The *fourth*, a nurse aged 20, who was only slightly anaemic, had developed diarrhoea whenever she took ferrous gluconate. The *fifth*, aged 55, who suffered from hereditary haemorrhagic telangiectasia with some blood loss, had felt epigastric discomfort and anorexia whenever she took a colloidal iron preparation. These patients took ferrous fumarate with benefit and without side-effects. The *sixth* patient, while intolerant of four other iron preparations, was also intolerant of ferrous fumarate, and is described below because, in addition, she failed to respond to it.

3. Failure to Respond to Ferrous Fumarate

Alone of all the patients given ferrous fumarate one woman made no response whatsoever during the fortnight she was treated. She was aged 54, and since the age of 18 had received 12 blood transfusions and four courses of parenteral iron, which had helped her greatly. She had taken iron many times before, and iron by mouth had never helped her but had often made her sick. When given ferrous fumarate as a trial of its side-effects, her haemoglobin was 9.3 g./100 ml. (63%) and the red cells were microcytic and hypochromic. She took ferrous fumarate three times daily, but felt nauseated much of the time and vomited within two hours of taking most tablets. This nausea and vomiting continued until the tablets had to be stopped at the end of two weeks, the haemoglobin remaining at 9.3 g./100 ml. and the film showing no evidence of an influx of normochromic cells. She persisted with treatment for as long as she did because of her apparently genuine desire to co-operate. The haemoglobin responded well to a subsequent course of iron dextran given intramuscularly, rising to 13.6 g./100 ml.

4. Post-gastrectomy Iron Deficiency

The responses were followed of four patients on whom partial gastrectomy had been performed for peptic ulceration some years previously and who had developed iron-deficiency anaemia.

The first two patients, whose operations had been 8 and 10 years previously, responded well to ferrous fumarate and achieved normal and apparently maximum haemoglobin levels within eight weeks. The third patient whose operation had been seven years previously, responded very slowly, his haemoglobin level being 8.9 g./100 ml. at the start of therapy, rising to 12.3 g./100 ml. at eight weeks. Not until 13 weeks did it reach its top level of 15.4 g./100 ml. Examination of the stools of this patient was consistently positive for occult blood, but the source of the bleeding could not be identified without further surgery.

The fourth patient, whose partial gastrectomy had been four years previously had been taking colloidal iron medicine for two and a half years without clinical benefit and presented with a haemoglobin of 8.0 g./100 ml. and an M.C.H.C. of 26.8%. She did respond slowly to ferrous fumarate, but after five weeks her haemoglobin had risen to only 8.7 g./100 ml. Further investigations were therefore performed. These included a radio-iron absorption test, carried out after all other iron therapy had been stopped for one week. 0.66 g. of ferrous glycine sulphate labelled with ^{59}Fe (117 mg. of elemental iron) was taken by the patient, and all stools were collected until they contained no more significant radioactivity. The faecal recovery was 49% of the ingested dose of radio-iron. When the radio-iron absorption test was completed she was given 100 mg. of elemental iron in the form of ferrous fumarate. One and a half tablets of this were mixed with water, in which they formed a suspension in a matter of seconds, and this was taken fasting. The serum iron was estimated before and again two hours after this dose and was found to have risen from 20 to 102 μg./100 ml. Stool examination for occult blood was positive at this time. Treatment was then resumed with ferrous fumarate, and the haemoglobin continued to rise slowly.

5. Histamine-fast Achlorhydria

Only two patients are known to have a histamine-fast achlorhydria. They responded as satisfactorily as the others.

Discussion

It is of interest that the response to ferrous fumarate was as good for the group of "complicated" iron deficiencies as for the uncomplicated group, all the patients being unselected initially so long as they were anaemic and showed red-cell hypochromia. It is obvious, nevertheless, that there will be a limit to the amount of current blood loss or "toxic" influence which can be borne by a patient without it depressing the response to iron therapy.

Although no controls have been provided with this series, the results have been presented in a way which should allow of comparison with other series of patients treated with iron compounds who have been followed by the percentage rise of haemoglobin in the peripheral blood. Such estimations—for example, those shown in Fig. 2—do not necessarily reflect accurately the whole haemoglobin production of the bone marrow, as was well shown by Whitby (1949), who demonstrated that considerable adjustments are made to the total circulating haemoglobin which are not reflected by the percentage haemoglobin levels of the peripheral blood. Fig. 2, however, allows one to estimate the expected rise of haemoglobin percentage in a patient about to start ferrous fumarate therapy.

The response to ferrous fumarate has not been summarized in terms of percentage rise of haemoglobin per day. If Fig. 2 is studied it can be seen that the average rise in haemoglobin per day for the same group of patients can be made great or small according to the number of weeks over which the average is taken. Another important variable is the rise in haemoglobin per day in the severely anaemic patients, which is greater than in the less affected. Such variables make it difficult to describe the results of a clinical trial of iron therapy by a simple figure, applicable to all cases, in terms of haemoglobin rise per day. This adds to the difficulty of comparing quantitatively the results obtained by different workers. The method of presentation used here can be applied without modification to any similar series provided that the haemoglobin level has risen to near maximum by eight weeks. An iron preparation which does not achieve this condemns itself *ipso facto*.

The simplest comprehensive description of the response of the haemoglobin level to the drug is the curve given in Fig. 3, and the existence of such a curve is of considerable interest. Such a single curve has provided a rational basis for summarizing the results of the present trial. Thus the mean percentage of the return to "normal"—that is, the eighth-week value—achieved at any stage of therapy may be read off the

curve at once, without regard to the initial haemoglobin. For example, about the 18th day of treatment the haemoglobin levels of all groups of patients had returned exactly halfway to normal. It has not yet been shown that the result of therapy with other forms of oral iron can be characterized by a single curve, but there is no reason apparent why this should not be possible.

Having fitted a single curve to depict the therapeutic response of a series of cases, it is still a difficult matter statistically to measure the differences between two or more such curves. Accordingly the mean proportionate return to normal of a group of patients after three weeks ("p" in Analysis 2) has been recommended as an appropriate and simple measure of success, suitable for assessing the results of such a trial as this. It is based on the potential existence of the common curve, but does not demand its construction, and requires only three haemoglobin readings in all, on each patient, but the timing of these must be uniform. The end of the third week was chosen arbitrarily as being a convenient time near the halfway figure.

Fig. 3 draws attention to the fact that mild anaemias appear to need as prolonged therapy as the more severe anaemias. This fact may be explained in part by the way in which the amount of iron absorbed from the gut is proportional to the degree of erythropoesis in the bone marrow as shown by Bothwell, Pirzio-Biroli, and Finch (1958). These workers also showed that depletion of iron stores is associated with an increased absorption of iron from the gut. Unlike erythropoiesis, this influence should be uniform in the patients of the main series here, who can all be presumed to have had depleted iron stores. Anaemia *per se* does not appear to be a controlling factor in iron absorption (Pirzio-Biroli, Bothwell, and Finch, 1958). Although the haemoglobin levels were effectively normal by the eighth week (Fig. 2), the fact that they were still climbing slightly would suggest that more prolonged therapy is indicated. We consider, for routine treatment, that a three-months course of iron therapy by mouth is the minimum for any iron-deficient patient regardless of the initial haemoglobin level. This recommendation is directed towards the treatment of the anaemia and takes no account of the need for building up iron reserves.

There is a point of interest in the close similarity between the curves in Fig. 2 and those in Chart 2 of the publication by Isaacs, Bethell, Riddle, and Friedman (1938), where the curves represent the average rate of formation of red cells in patients with pernicious anaemia after treatment with intramuscular liver extract. These authors point out that a red blood cell count of 5,000,000/ c.mm. may be expected at the end of eight weeks, regardless of the initial count. Although iron and vitamin B_{12} seem to have such different points of action it appears that there may be some governing factor which is common to both and determines this common pattern of response.

Patients who are iron-deficient after partial gastrectomy usually respond satisfactorily to iron therapy by mouth (Baird, Blackburn, and Wilson, 1959), and this was shown in the present series by two patients whose rise in haemoglobin corresponded to the figures represented in Fig. 2. There were two examples of a slow response related, at least in part, to alimentary blood loss. Ferrous fumarate was slowly effective therapeutically in both these patients, one of whom had failed to respond at all to a colloidal iron preparation. This patient absorbed radio-iron well and showed evidence of a satisfactory absorption of iron given as ferrous fumarate, despite her slow clinical response. Baird *et al.* (1959) have shown in 38 patients who were suffering from post-gastrectomy iron-deficient anaemia that prolonged treatment with iron (mean time 6.5 months) was often required even in the absence of alimentary bleeding.

Only one patient among the 64 treated failed to respond at all to ferrous fumarate. This patient appears to be suffering from iron malabsorption, although this has not yet been proved. The cause of the apparent malabsorption was not known at the time of the trial, but the patient had been treated successfully for lupus vulgaris seven years before. The gastric irritation caused by the tablets seemed genuine.

Only two patients in the series are known to have a histamine-fast achlorhydria. Since they responded to ferrous fumarate as promptly as the others it would suggest that hydrochloric acid is not essential to the absorption of the iron from ferrous fumarate any more than it is for ferrous ammonium sulphate (Grace, Doig, and Wolff, 1954), or for iron incorporated into the chemical structure of foodstuffs (Moore, 1955). This *in vivo* observation is of interest, since tablets of ferrous fumarate are more soluble *in vitro* in dilute hydrochloric acid than they are in water.

The incidence of toxicity and side-reactions over the whole group of 64 patients treated was low. Only the patient just referred to who had presumptive malabsorption of iron had nausea and vomited, and it seems debatable whether the toxic response of such a person is used justifiably as a criticism of a drug which is so conspicuously free from troublesome side-effects in all the patients who did respond. Only 2 out of the remaining 63 patients reported mild epigastric discomfort for the first 10 days on treatment.

It would seem that ferrous fumarate tablets, which disintegrate so rapidly in the mouth, may thereby make a material contribution to the treatment of those patients who cannot swallow tablets and who have formerly had to take liquid iron preparations or receive iron parenterally. In addition it makes available an iron preparation which has a very low incidence of gastro-intestinal side-effects, which, when present, are mild.

Summary

All of 55 patients suffering from untreated iron-deficiency anaemia and forming the main series in this investigation responded well to ferrous fumarate, 200 mg. (one tablet) three times daily. Nine other patients were given ferrous fumarate for reasons described.

Of the 63 patients who responded to ferrous fumarate, 2 (3%) complained of mild epigastric discomfort for 10 days. The remaining patient, who did not respond and who had presumptive iron malabsorption, had more marked gastric symptoms. Eight patients giving a history of alimentary disorder when taking other iron preparations accepted ferrous fumarate without a symptom. Four patients suffering from post-gastrectomy iron-deficiency anaemia are described separately. Two of them responded very slowly to treatment.

The haemoglobin figures in the main series have been subjected to two analyses. The first shows that the responses to therapy of all the patients can be expressed by a common curve without regard to the degree of the initial anaemia. The existence of this curve establishes the importance of continuing iron therapy for as long a time in mild anaemia as in severe cases and demonstrates that this should be for more than two months.

The second analysis is based on the establishment of this common curve. The mean percentage recovery attained by the end of the third week was 59%, with a statistical accuracy for the mean of ± 4.8. It is suggested that this method of analysis and presentation of data with known statistical accuracy will allow of comparisons between trials of different iron preparations. The haemoglobin levels at the start of therapy, after three weeks, and on reaching normal are required for this method of analysis.

The willingness with which patients were referred for treatment by the consultants of the hospitals concerned, by their staffs, and by family doctors, is gratefully acknowledged. Dr. E. K. Blackburn, in whose department the work has been carried out, has been particularly helpful at all stages. Dr. I. McLean Baird kindly performed the radio-iron study in one case. Thanks are also due to Mr. J. Monaghan and Miss Joan Ripley for technical help; to Mr. A. Howard; to the Board of Governors of the United Sheffield Hospitals for a research grant; and to Mrs. W. M. Wright and Miss D. Kirk for computational assistance. Glaxo Laboratories Ltd. kindly supplied tablets for the trial and have assisted in other ways.

Statistical Appendix

Analysis 1

Lines of regression of haemoglobin at the week (k) on initial haemoglobin were fitted for k=1 to 8 inclusive and for the two categories of patient (simple and complicated iron deficiency) and the standard errors of their coefficients were estimated. Differences between slope and differences between positions of the lines for the two categories of patient were compared with their standard errors, and in no case proved statistically significant at the 5% level, therefore a single regression was computed for each week, the categories being combined. The regressions for the different weeks were of course subject to sampling errors, which were largest for k=5 and 7, for which only a few records were available.

The method of analysis first adopted was to fit curves of suitable exponential type to the slopes of the regression lines; and to their heights at 59.

Curves were fitted by weighted least squares (weights being inversely proportional to sampling variances) and provided approximate χ^2 criteria of goodness of fit of 2.27 and 11.69 respectively, each with six degrees of freedom. The failure of these to attain the 5% level of significance, along with the apparent lack of trend in the deviations from the fitted curves, confirmed the adequacy of these curves as a summary of the data, and curves of the form shown in Fig. 2 were deduced from them. However, it was noted that when these were re-scaled, as in Fig. 3, they became almost identical, and it was therefore decided to fit curves to slope and height which were related in such a way as to give a single curve as shown in Fig. 3. This was done by an approximation to least squares. The corresponding joint χ^2 criterion was 9.83, with 13 degrees of freedom, indicating a fit which was not only satisfactory but better than before. This seems paradoxical until it is remembered that the new curve fitted to heights comes from a more complicated mathematical family than appeared to be necessary for the first analysis, and is thus more flexible.

Evidently there are adequate grounds for summarizing the data by the curve of Fig. 3.

Analysis 2

The three observations required for computing p were available in 27 cases. In 26 of the remainder, either x_3 or x_8 was not available, and the following expedients were adopted as necessary: (1) x_3 interpolated between observed values—for example, $\frac{1}{2}(x_2+x_4)$, or $\frac{2}{3}x_2+\frac{1}{3}x_5$—a procedure justified by the approximate straightness of the curves of Fig. 2 over the range one to six weeks. (2) x_7 used in place of x_8, with a slight adjustment, using the appropriate curve of Fig. 2. (3) x_8 estimated entirely from the appropriate curve of Fig. 2.

In two cases the data were insufficient for the application of these expedients, and were therefore not used.

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PARTIAL THORACIC STOMACH IN CHILDHOOD

BY

JOYCE B. BURKE, M.D., M.R.C.P., D.C.H.

From the Thoracic Unit, the Hospital for Sick Children, Great Ormond Street, London

The condition known as congenital short oesophagus, hiatus hernia, or partial thoracic stomach has interested paediatricians and surgeons only comparatively recently. It is clear from the work of Carré *et al.* (1952) that the course is generally benign, symptoms subsiding after the first year or two of life in the majority of children, though it seems probable that they may recur in adult life. Unfortunately, not all cases pursue this favourable course, and vomiting may continue intermittently for years. Stricture formation is the main complication to be feared, but as yet there is no evidence to show that prompt treatment reduces the incidence of this complication or whether it may be predicted. The part that surgery has to play in management is still undecided. The purpose of this paper is to present an analysis of the cases of partial thoracic stomach attending the Hospital for Sick Children, Great Ormond Street, over a period of 10 years. Most of these cases were included in an interim report by Waterston (1954).

Material

During the 10 years 1945 to 1955 137 children attending the hospital were diagnosed as having partial

thoracic stomach, and 132 of these had a small intrathoracic loculus of stomach. In the other five the hernia comprised most of the stomach, and, as the problems presented were rather different, they are considered separately. Only cases followed up for longer than nine months have been included. In Table I the duration of the follow-up period is shown.

TABLE I.—*Duration of Follow-up of 137 Cases of Partial Thoracic Stomach*

	Follow-up Period (Years)							
	<1	1–2	2–3	3–4	4–5	5–7	7–10	10
No. treated medically ..	13	13	8	17	8	4	2	3
No. treated surgically ..	4	7	13	14	15	8	5	3
Total ..	17	20	21	31	23	12	7	6

Sex and Familial Incidence.—There were 97 boys and 35 girls in this series—that is, a male : female ratio of 2.7 : 1. The disease was more severe in the males, half being below the third percentile in weight when first seen, compared with one-quarter of the females. Thirty-three children (25 males and 8 females) had a stricture. The mother and sister of one child were found to have a partial thoracic stomach, the sister having attended the hospital 12 years previously on account of vomiting. Twin boys were both affected. The brother of another child was operated on elsewhere for an oesophageal stricture. A history of vomiting in parents and siblings was often obtained but was not followed up.

Symptomatology

Vomiting.—The typical history was one of vomiting from birth. Birth was given as the time of onset in 102 children (77%), and in a further eight vomiting started within the first month of life. In the remaining 22 the age at onset was given as between 1 and 3 months in five, between 3 and 6 months in six, between 6 and 12 months in five, and in six the onset was after 1 year of age. Vomiting might be projectile. Thirteen of these children had been operated on for suspected pyloric stenosis, and a pyloric tumour was found in three. A study of the case histories revealed a very characteristic sequence of events. In uncomplicated cases improvement began with the introduction of solids, and vomiting was infrequent after the first year. The mother often remarked that vomiting ceased completely when the child began to walk, but it was common for vomit to be found on the pillow at night for some weeks after it had ceased in the day. Laughing or jolting was noticed to precipitate vomiting. With stricture formation the pattern changed and vomiting tended to become episodic, attacks lasting for several days being interspersed with periods of comparative freedom, dysphagia gradually becoming the predominant symptom, and difficulty in making the child take solids the mother's main problem.

Haematemesis occurred in 117 (89%), of the 132 children with a small intrathoracic loculus of stomach, and in eight it was associated with melaena. Altered blood was often seen mixed with mucus in the vomit within a few days of birth. Its presence is highly significant, because vomiting at this age is very common; but haematemesis, apart from the regurgitation of swallowed blood in the first day or two of life, is unusual. A large haematemesis was exceptional. Considerable bile-staining of the vomit was noticed in two cases. The absence of constipation, coupled with the frequency of haematemesis, is an important point in the differentiation of partial thoracic stomach from pyloric stenosis in an infant presenting with vomiting and unsatisfactory weight gain.

Dysphagia was an ominous symptom, usually the culmination of a sequence of events such as the following. The mother would say that when the infant was offered thickened feeds between 3 and 6 months of age vomiting became less, but solids such as biscuit and bread resulted in choking. She waited for a time and then tried again, with the same result; and so the infant continued on a milk and purée diet, and finally advice was sought on account of dysphagia with solids when he was about a year old. In some cases vomiting persisted as the predominant symptom and dysphagia was not clearly distinguished from it. Dysphagia was noted in 50 out of 132 cases (38%), and was associated with radiological evidence of narrowing of the oesophagus in 40. In 10, free reflux only was present. For the purpose of this review each case has been placed in one of four clinical groups at the time of follow-up (Table II). Group 4 includes four children who died. It will be seen that dysphagia was of considerable prognostic importance, for only 11% of the children who were symptom-free had complained of dysphagia, as compared with over 70% of those with fairly severe and very severe symptoms—that is, cases in groups 3 and 4.

TABLE II.—*Prognostic Significance of Dysphagia*

	Group 1	Group 2	Group 3	Group 4
Clinical grouping of 132 cases	65	44	10	13
No. with dysphagia ..	7 (11%)	26 (59%)	9 (90%)	8 (61%)

Group 1: Symptom-free at time of follow-up.
Group 2: Mild symptoms only at time of follow-up.
Group 3: Symptoms fairly severe, but tendency to improvement at time of follow-up.
Group 4: Persistent severe symptoms at time of follow-up.

Weight.—The weight of these children was generally well below average when they first presented, the majority falling below the fiftieth percentile. Severe dehydration was occasionally present, especially during the early weeks of life. Of the 132 children, 59 were below the third percentile on their first visit to the hospital; 50 of these were boys and 9 were girls. At their first attendance 85 children were under 1 year of age, and only four of these had reached the fiftieth percentile. It follows, therefore, that partial thoracic stomach is unlikely to be the cause of vomiting in an infant whose gain in weight is average, or above average.

Anaemia may be due partly to loss of blood and partly to malnutrition. Of the 132 children, 112 had an oesophagoscopy and haemoglobin estimation done at about the same time, and Table III shows that the degree of anaemia is related to the severity of oesophagitis.

TABLE III.—*Degree of Anaemia Related to Severity of Oesophagitis in 112 Cases*

Haemoglobin Level	Oesophagitis on Oesophagoscopy		
	None	Mild	Severe
<50%	1	0	6
50–65%	6	5	18
65–80%	12	10	14
>80%	21	9	10

Diagnosis of Partial Thoracic Stomach and Oesophageal Stricture

Radiological Appearances.—Hodson (1954) has pointed out that while radiological diagnosis of advanced cases with persistent oesophageal narrowing and oesophagitis is comparatively easy, uncomplicated cases may present difficulties in diagnosis owing to the wide range of normal variation. It is now recognized that partial thoracic stomach may cause no symptoms, and Astley (1954) states that it can be present in the absence of demonstrable gastro-oesophageal reflux. According to Hodson (1954), reflux of gastric contents into the oesophagus is seen in barium studies of normal infants, though this is denied by Husfeldt (1953). At all events, most authorities are agreed that even when symptoms are found associated with radiological evidence of reflux, *x*-ray examination may need to be repeated several times before a loculus of stomach can be visualized above the diaphragm, and rapid serial pictures are very helpful in this demonstration. Most of the patients referred to the hospital with symptoms suggestive of partial thoracic stomach respond satisfactorily to simple medical measures and are not subjected to further barium studies if the first is inconclusive. Such patients were, of course, not included in the present series. In contrast, oesophageal narrowing associated with oesophagitis or organic stricture is unlikely to be overlooked even in an uncooperative child. These factors probably account for the high incidence of complicated cases in this series (45%).

Oesophagoscopy gives valuable information about the state of the oesophageal mucous membrane and the presence or absence of stricture formation. The oesophagus may be filled with acid or alkaline fluid, and reflux often occurs during the examination. In any one case the appearance on oesophagoscopy was found to vary considerably at different examinations. Table IV shows the severity of oesophagitis on the first examination in relation to clinical condition at the time of the follow-up in 110 children on whom oesophagoscopy was performed. The majority were symptom-free or had mild symptoms only, and were placed in groups 1 and 2 regardless of the severity of oesophagitis initially, but persistence of oesophagitis was of ominous significance, as it finally led to the formation of a stricture.

Prognostic Significance of Narrowing of the Oesophagus

The term "stricture" implies narrowing, which in the case of the oesophagus may be due to spasm of the muscular wall or to fibrous contracture. The diagnosis of narrowing can be made radiologically, by oesophagoscopy, and at operation. If persistent narrowing of the oesophagus with dilatation above is accompanied by rigidity of walls and hold-up of thick barium, there is no doubt that organic stricture is present. On the other hand, narrowing of the oesophagus may be demonstrated which is inconstant and is probably due to spasm. Throughout this paper the term stricture is therefore used to imply organic fibrous contracture and the other cases are referred to as "oesophageal narrowing."

Table V shows the clinical grouping of the cases at the time of the follow-up in relation to the presence or absence of oesophageal narrowing and organic stricture. In 72 cases there was no evidence of oesophageal narrowing. Six of these children were mentally retarded and account for two of the four placed in groups 3 and 4. Thirty-three children had an organic stricture. Operation was carried out in 25, and in 13 no stricture was demonstrable at the time of the follow-up. This group of 33 included four mentally retarded children who were placed in groups 3 and 4. Narrowing of the oesophagus was found radiologically or on oesophagoscopy in 27 children, but was not persistent. Twenty were operated on, and in nine no narrowing was present at the time of follow-up.

It will be seen from Table V that 94% of the children with no evidence of oesophageal narrowing were placed in groups 1 and 2. In contrast, 69% of those with organic stricture and 67% of those with variable oesophageal narrowing were placed in groups 1 and 2. These figures indicate that the presence of variable narrowing or organic stricture of the oesophagus materially alters the prognosis.

TABLE V.—*Prognostic Significance of Oesophageal Narrowing and Organic Stricture*

	Total	Group 1	Group 2	Group 3	Group 4
No oesophageal narrowing ..	72	51 (70%)	17 (24%)	2 (3%)	2 (3%)
Organic stricture	33	3 (9%)	20 (60%)	3 (9%)	7 (22%)
Variable oesophageal narrowing	27	10 (37%)	8 (30%)	5 (18%)	4 (15%)

Association of Partial Thoracic Stomach with Other Conditions

Pyloric Stenosis.—In 13 cases laparotomy was performed for suspected pyloric stenosis in this hospital or elsewhere, and a tumour was found in three. In one child a pyloric tumour was felt at the age of 3 years when he had developed a stricture. The association of partial thoracic stomach and pyloric stenosis has been noted before (Smellie, 1954), and it may well be that any condition giving rise to vomiting will aggravate or initiate the symptoms of an existing hiatus hernia. Olsen and Harrington (1948), reviewing 220 cases of "short oesophagus" in adults seen at the Mayo Clinic, noted an apparent aetiological factor in 78%, and in almost one-third of these it was some condition giving rise to vomiting. An attack of whooping-cough caused an exacerbation of symptoms in several of our cases.

Abnormalities of the glottis or trachea causing stridor occurred in five children, and on one of these severe

TABLE IV.—*Clinical Condition at Time of Follow-up Related to Severity of Oesophagitis on First Examination* (110 *Cases*)

Treatment	No Oesophagitis				Mild Oesophagitis				Severe Oesophagitis			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Medical ..	12	10	0	0	5	8	1	0	10	4	1	3
Surgical ..	7	9	1	0	4	2	2	2	10	11	2	6
Total ..	19	19	1	0	9	10	3	2	20	15	3	9

stridor during the induction of anaesthesia necessitated tracheotomy, and the operation for repair of her hernia was abandoned. Cleft of the soft palate was associated with partial thoracic stomach, sucrosuria, and mental defect in one child.

Mental retardation was present in 10 children; two of these had phenylketonuria and four sucrosuria. One child with phenylketonuria and severe mental and physical retardation presented at the age of 3½ years with a tight fibrous stricture. She died a year later in another hospital, and at post-mortem examination a large oesophageal ulcer was found.

Moncrieff and Wilkinson (1954) have described the association of sucrosuria, mental defect, and hiatus hernia. The three conditions were present together in four cases in this series.

Management of Partial Thoracic Stomach in Childhood

Table VI relates the age at which the child first attended the hospital to the clinical category at the time of follow-up. It shows that the prognosis in children presenting under the age of 1 year is very good. Of 81 cases, 74 (91%) were placed in groups 1 and 2. Only four of the 61 children who first attended under the age of 6 months have been placed in groups 3 and 4. Two of these had a stricture when first seen (one died of gastro-enteritis in another hospital). The third child was severely retarded mentally with sucrosuria and a cleft-palate. The fourth child first attended at the age of 5 months with a large hernia and was treated surgically. Symptoms persisted and the hernia was found to have recurred. She was awaiting a second repair at the time of writing.

TABLE VI.—*Prognosis Related to Age at Which Child First Presented*

Age at 1st Attendance	Total	Group 1	Group 2	Group 3	Group 4
<6 months ..	61	44	13	2	2
6–11 ,, ..	20	8	9	1	2
1 year	32	12	12	2	6
2 years ..	4	0	3	1	0
3 ,, ...	5	1	1	1	2
4 ,, ...	2	0	1	1	0
5–7 ,, ...	4	0	2	2	0
8–10 ,, ..	3	0	2	0	1
>10 ,, ..	1	0	1	0	0
<1 year ..		90%		10%	
>1 ,, ..		70%		30%	

There are two possible conclusions to be drawn from these findings. Early treatment, whether medical or surgical, may prevent the occurrence of oesophagitis and stricture formation. On the other hand, as it seems probable that the majority of untreated cases recover spontaneously (Carré *et al.*, 1952) it may be that those presenting later would not have responded to treatment even had it been instituted in the first few months of life. Against this latter suggestion we have no uncomplicated cases presenting under the age of 6 months, and adequately treated, who have not done well.

Medical Treatment

Medical treatment is satisfactory in most cases of partial thoracic stomach. The infant is maintained in as near an upright position as possible throughout the day and night in a chair specially constructed for the purpose, and feeds are thickened if necessary. In untreated cases improvement usually follows the introduction of solids, and symptoms often cease altogether when the child gets on to his feet. Carré *et al.* (1952) state that after symptomatic improvement the partial thoracic stomach persists unchanged, though reduced or absent reflux makes it more difficult to demonstrate. Husfeldt (1953) observed 25 cases treated medically, and the hernia disappeared in seven. In the present series follow-up barium studies were not made routinely. Fifty-three cases of partial thoracic stomach showing no evidence of stricture formation or oesophageal narrowing were treated medically. *X*-ray findings remained unchanged in 23, and 11 of these were symptom-free at the time of the follow-up In 11 the hernia disappeared, and 8 of these were symptom-free. In 19, follow-up *x*-ray examinations were not carried out.

Sixty-eight children were treated medically—in 53 there were no complications, 8 had organic strictures, and 7 had variable oesophageal narrowing. Table VII shows the clinical grouping at the time of follow-up. Two of the three cases in group 4 were severely retarded mentally, and one child, mentioned previously, died of gastro-enteritis in another hospital. Of those treated medically, 90% were placed in groups 1 and 2 at the time of follow-up.

TABLE VII.—*Clinical Grouping at Time of Follow-up of Cases of Partial Thoracic Stomach Treated Medically*

	Total	Group 1	Group 2	Group 3	Group 4
Uncomplicated cases	53	38	13	1	1
Organic stricture ..	8	0	6	1	1
Cases with variable oesophageal narrowing	7	3	2	1	1
Total	68	41 (60%)	21 (30%)	3 (5%)	3 (5%)

Surgical Treatment

The question arises whether surgery plays any part in the management of partial thoracic stomach in childhood, and, if so, the best time for surgical intervention. Opinion is divided on this subject. Stricture formation is the main complication. It is presumed that reflux of gastric juice into the oesophagus causes erosion of the mucous membrane, and chronic inflammatory changes result in fibrous contracture. There is no doubt that this process can take place over a very short period of time. Four children presented under the age of 7 months with a stricture, the youngest being 2 months old.

The aim of the operation carried out at this hospital is to restore the normal anatomy so far as is possible by reduction of the hernia and narrowing of the hiatus. By this means the normal angle of insertion of the oesophagus into the stomach is at least partially restored. If a stricture is present it is dilated via the stomach at the time of operation.

Of the 64 children subjected to surgery, 38 had some narrowing of the oesophagus demonstrated radiologically or on oesophagoscopy before operation—organic stricture was present in 25 and variable oesophageal narrowing in 13. In recent years the number of uncomplicated cases treated surgically has steadily declined, especially in children under 1 year of age. The clinical grouping of the cases treated

surgically is shown in Table VIII. The number of children in each group under 1 year of age at the time of operation was: group 1, 7; group 2, 8; group 3, 0; and group 4, 1.

In 19 cases treated surgically the partial thoracic stomach was uncomplicated or was accompanied by mild oesophagitis only. At the time of the follow-up 13 were placed in group 1 and 4 in group 2. The one

TABLE VIII.—*Clinical Grouping at Time of Follow-up of Cases of Partial Thoracic Stomach Treated Surgically*

	Total	Group 1	Group 2	Group 3	Group 4
Uncomplicated cases	19	13	4	1	1
Organic stricture ..	25	4	13	2	6
Cases with severe oesophagitis ..	20	7	6	4	3
Total	64	24 (38%)	23 (35%)	7 (11%)	10 (16%)

child in group 3 had persistent symptoms, and a loculus of stomach was still present above the diaphragm after operation. She is waiting a second repair. A severely retarded child with phenylketonuria was placed in group 4.

An organic stricture was found at operation in 25 cases. In 13 a stricture was no longer demonstrable at the time of the follow-up and all were placed in groups 1 or 2 except for one in group 3 who still had dysphagia and recurrent episodes of vomiting though usually able to take a normal diet. In six children some narrowing of the oesophagus was still present, five were doing well and satisfied the criteria for groups 1 and 2, and one was placed in group 3.

Six children with organic stricture at operation were placed in group 4. Two died of pneumonia, in two the stricture was excised but recurred, and two had persistent oesophagitis with severe symptoms in spite of a successful repair of the hernia.

In 20 children operation was done on account of severe oesophagitis. Oesophageal narrowing was present before operation in 13. At the follow-up 7 were placed in group 1, 6 in group 2, 4 in group 3, and 3 in group 4 (including one mongol). The hernia recurred in one mentally retarded child operated on at the age of 2 years and a second operation was considered, but 18 months later he began to improve and at the follow-up when 6½ years old he was symptom-free.

During the past year oesophago-gastrectomy has been carried out on seven of the children placed in groups 3 and 4.

It is noteworthy that in only 12 cases was there an immediate response to operation with cessation of symptoms. In the others improvement had sometimes begun before surgery was undertaken, but more often it was not evident until months or even years afterwards. This makes it difficult to assess the value of surgery. The fact that vomiting readily becomes habitual in children may partly explain the delayed response to treatment in some cases.

If two children whose hernia recurred after operation and two with severe mental defect are excluded, 11 out of a total of 64 children (17%) appeared to derive little or no benefit from repair of the hernia. An organic stricture was present before operation in five and severe oesophagitis with or without oesophageal narrowing in six. Three of these developed an organic stricture after operation.

Cases with a Large Intrathoracic Loculus of Stomach

In five children the cardia was found to be above the diaphragm, with a large loculus of stomach lying in the right chest. These cases had certain features in common; all were girls, the intrathoracic loculus of stomach could be seen on straight *x*-ray examination of the chest, and four were severely anaemic. The response to operation was immediate, with complete relief of symptoms.

Discussion

The difficulties encountered in evaluating the role of surgery in cases of partial thoracic stomach have been mentioned. As symptoms probably subside spontaneously in most cases the age at which the child first presents is obviously of great importance and also his age at the time of operation. The clinical condition bears no close correlation to the findings on oesophagoscopy and barium swallow, and throughout this paper there has been repeated reference to the clinical classification based on symptomatology and general health. Operation was performed on the majority of children with persistent oesophagitis; for this reason we are not able to compare the results of medical and surgical treatment, and our conclusions can only be tentative.

It is felt that cases presenting without evidence of oesophageal narrowing should be treated medically, but must be kept under close supervision. If symptoms are controlled and the gain in weight is satisfactory frequent barium studies and oesophagoscopies are unnecessary. Unsatisfactory gain in weight, haematemesis, anaemia, and dysphagia are indications that all is not well, even if the mother reports that vomiting is subsiding. In such cases oesophagoscopy is carried out periodically, and persistent oesophagitis with or without narrowing of the oesophagus is taken as an indication for surgery. Cases presenting with a stricture and oesophagitis, and those with a large intrathoracic loculus of stomach, are subjected to operation without delay.

Older children who have organic strictures *without* oesophagitis are treated conservatively by oesophageal dilatation as required. There were eight such children in the present series and two were mentally retarded. Though these children suffer the severe handicap of dysphagia the tendency is towards improvement as they grow older.

The children with severe persistent oesophagitis due to gastro-oesophageal reflux present the greatest problem in management, whether they have a stricture or not. Eleven such children derived no benefit from surgical repair of the hernia. Their lives were punctuated by recurrent admissions to hospital for treatment of vomiting, and intravenous fluids were often necessary to correct dehydration. Nutrition was impaired and anaemia invariably present in spite of iron therapy and blood transfusion. During the past year oesophago-gastrectomy has been carried out on seven of these children, and the immediate results of the operation are encouraging.

The clinical features of partial thoracic stomach in childhood have again been stressed, for prompt postural treatment undoubtedly relieves symptoms in young infants and probably reduces gastro-oesophageal reflux. An infant who consistently fails to thrive is best referred to hospital for investigation, and it should

be remembered that peptic ulceration of the stomach and duodenum is very rare in early childhood and the oesophagus is the most probable site of the bleeding in a young child with haematemesis.

Summary

The symptomatology, diagnosis, and management of 137 children with partial thoracic stomach are discussed. The main symptoms in 132 with a small intrathoracic loculus of stomach were vomiting (dating from birth in 77%), haematemesis (89%), dysphagia (38%), and unsatisfactory gain in weight. Males predominated by 2.7:1 and were more severely affected than females.

The prognosis in children presenting under 1 year of age was very good in 91%. Dysphagia and narrowing of the oesophagus were of serious prognostic significance.

Organic fibrous contracture of the oesophagus was present in 33 children, in 27 there was variable oesophageal narrowing, and in 72 there was no oesophageal narrowing (uncomplicated cases).

Of the 10 children who were mentally retarded, two had associated phenylketonuria and four had sucrosuria.

Sixty-eight children were treated medically and 64 surgically. The results are discussed. It is concluded that persistent oesophagitis with or without stricture formation is an indication for repair of the hernia. Uncomplicated cases and older children with strictures are given a trial of medical management.

Five children, all girls, had a large right-sided intrathoracic loculus of stomach and were symptom-free after surgery.

I thank Mr. D. J. Waterston and Professor R. S. Pilcher for permission to publish these cases; the physicians at the Hospital for Sick Children, Great Ormond Street, who referred cases under their care to the thoracic unit; and Dr. J. Sutcliffe and Dr. J. W. Wells, who did the fluoroscopies. I am especially indebted to Dr. R. E. Bonham-Carter, who suggested this review and gave much advice and encouragement.

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Dr. Aleksandra Taylor, a Polish child-specialist who has been awarded a British Council bursary for two months' study here, derives her name from a Scottish "soldier of fortune" who fought in the religious wars in Poland. During the seventeenth century large numbers of Scots emigrated to Poland and took part in commerce or became craftsmen. An interesting booklet entitled *Scots in Old Poland*, and published for the Scottish-Polish Society by Oliver and Boyd Ltd. in 1941, says, "For centuries Scotland had been the recruiting ground of mercenaries for all nations . . . in the last three decades of the sixteenth century we find definite information of Scottish soldiers and officers engaged in the Polish service." In the year 1775, according to this booklet, the name Tayler (Taylor) is found among the list of enrolled officers.

CRANIOSTENOSIS

BY

H. GORDON, M.B., B.Ch., D.C.H.

Johannesburg

Craniostenosis is a not uncommon condition of skull deformity caused by premature fusion of the sutures with consequent cessation of growth. The term was introduced by Virchow in 1851, although the condition had been known for a long time, and Bachman (1908) stated that the deformity and its relationship to the sutures were known to both Hippocrates and Galen. There is an extensive literature, mostly containing case reports and reviews of the literature, the reports usually citing severely affected cases, often with blindness. Only two large personal series have been reported, and these by neurosurgeons who have operated on them and presumably have seen selected cases: Ingraham, Alexander, and Matson (1948) reported on 50 cases, and McLaurin and Matson (1952) on 36 cases operated on in the first six months of life.

I have attempted to evaluate the seriousness and significance of the condition, and report here on 37 cases; these represent all the cases in Africans I have seen. They have been found by searching amongst the patients presenting at a paediatric out-patient clinic and at the casualty department of a hospital. In addition, approximately one-third were found at a social work centre. I have ensured that not only gross cases were picked out, and it is significant that not one of these cases has presented with complaints related to the craniostenosis. Thus these cases represent an unselected series, and analysis should therefore approximate to the true picture of the disease.

Normal Skull and Brain Growth

The skull grows secondarily to the brain; should the brain fail to grow, as in microcephaly, so will the skull. And where brain size becomes excessive, as in hydrocephalus, so does skull size. Indeed, the digital markings normally found in skull *x*-ray films in childhood suggest that the pressure caused by the growing brain stimulates skull growth. This growth occurs at the sutures, at right angles to them. Thus growth at the coronal suture is responsible for the length of the forehead, at the lambdoid suture for the length of the posterior head, and at the sagittal suture for its

Fig. 1.—Three cases of premature sagittal suture fusion showing elongation of the heads. The two outer boys are brothers. When viewed from above the middle portion of the head is narrow.

breadth (Figs. 1 and 2). Although growth ceases much earlier, the sutures do not normally fuse until after the twentieth year, and complete fusion may take several years (Todd and Lyon, 1924).

If one or more sutures fuse prematurely (Figs. 3 and 4), compensatory growth at unaffected sutures or fontanelles that are still open may occur. Where compensation is insufficient continuing brain growth leads to a rise in intracranial pressure which may have serious sequelae. Brain growth is independent of the skull and continues even in the presence of defective skull growth.

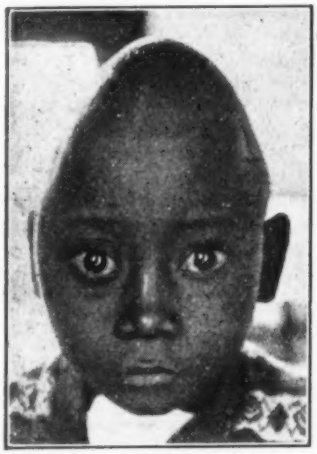

FIG. 2.—Coronal and sagittal suture fusion. Note compensatory growth at anterior fontanelle, and narrowness and asymmetry of head.

FIG. 3.—This patient was first seen on the pavement when I drove past. Two of his siblings have craniostenosis. Note exophthalmos and poor facial development.

The brain grows maximally in intrauterine life; in postnatal life, from the figures of Coppoletta and Wolbach (1933), it can be seen that its weight at birth is almost doubled at 6 months and practically trebled at 1 year. Between 1 year and 3 years it increases its weight by 23% and between 3 and 12 years by 19%. Simmons and Peyton (1947) state that after 3 years little increase in cranial capacity occurs, the skull size increasing because of bone-thickening and the development of accessory sinuses.

Diagnosis

The deformity of the skull is usually obvious and depends on the suture or sutures involved and the amount of compensatory growth at unaffected sutures, this depending on the age of onset of premature fusion. If more than one suture is involved the order of obliteration determines deformity.

Premature fusion when brain growth has ceased or is proceeding slowly leads to minimal deformity In some cases, usually of severe craniostenosis, facial development may be poor and the orbits shallow, leading to exophthalmos and occasionally even to dislocation of the eyeballs: this is presumably due to premature fusion of facial sutures. In other cases syndactylism and craniostenosis may be associated. This has led to the description of two syndromes, neither of which should be differentiated from craniostenosis — Crouzon's syndrome of hereditary cranio-facial dysostosis and Apert's syndrome of acrocephalo-syndactylism. Heredity and associated syndactylism are discussed below.

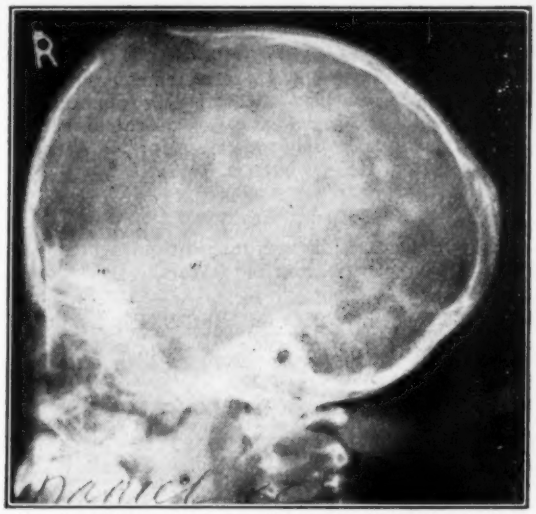

FIG. 4.—Radiograph at age of 6 years. Coronal and sagittal sutures fused. Note compensatory growth at anterior fontanelle.

X-ray examination confirms the diagnosis; affected sutures cannot be visualized (Fig. 5) and compensatory deformity is shown. There may also be increased digital markings, and, if the facial development is poor, accessory air sinuses may be absent or poorly developed. The *x*-ray picture makes it possible to identify the sutures involved and the many descriptive terms (scaphocephaly, oxycephaly, turricephaly, etc.) can be abandoned.

Incidence

In 1926 Greig stated that "oxycephaly is so uncommon that no observer can record from personal experience many cases of it." The term oxycephaly can be applied to about one-quarter of the cases of craniostenosis. Bolk (1915), in a report on the examination of 1,820 skulls, all but 58 those of individuals under 13 years of age, found complete sagittal suture fusion in 1% and partial fusion in 1½%; the coronal suture was fused in 0.33%. He also noted

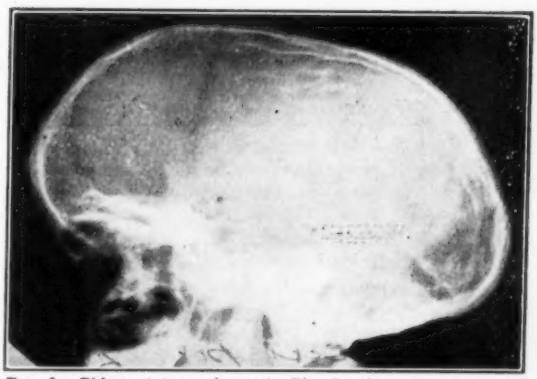

FIG. 5.—Eldest of boys shown in Fig. 1. Age when *x*-rayed 7 years. Note elongation of head. In antero-posterior view no sagittal suture is seen.

that the proportion of affected skulls was static after the seventh year, concluding that premature fusion always occurs before the age of 7.

My feeling is that Bolk's figures represent the true incidence, since in a play-school of approximately 600 African children I found six cases of craniostenosis. Despite this incidence only two case reports in Africans exist (Meyerson, 1957; Whittaker, 1958).

Clinical Features

Age.—In my cases the ages ranged from 7 months to 13 years, the majority being 3 to 6 years.

Sutures Affected and Sex Incidence.—Table I shows a preponderance of males; this is often recorded in the literature. The African female has short hair and the deformity is not hidden by elaborate hair styles; thus this possibility of error can be discounted.

TABLE I

Suture Involved	Males	Females	Total
Sagittal	15	8	23
,, and coronal	6	1	7
,, ,, lambdoid	1	1	2
Coronal ,, ,,	1	1	2
,,	1	—	1
Miscellaneous (*x*-ray films not entirely satisfactory)	2	—	2
Total	26	11	37

Associated Congenital Deformities.—These occurred in only two cases, both with premature sagittal suture fusion. A girl aged 12 had a high arched palate, spider fingers, and atrial septal defect, and a boy of 3 years had club-feet. Park and Powers (1920) and Ingraham, Alexander, and Matson (1948) report an increased incidence of congenital deformity in craniostenosis. Certainly an association exists between premature coronal fusion and syndactylism (Apert's syndrome).

Family History.—Owing to the method of case-finding and the instability of our urban African population, families could not easily be investigated. Nine families were investigated—the immediate family was examined and a careful history was taken of the remainder. In four families no familial incidence was found and the remaining five families are analysed in Table II. Further evidence of the unity of craniostenosis is found, as different sutures may be affected in siblings. There is a strong hereditary tendency, which, I feel sure, fuller investigation would confirm. Gates (1946) has reviewed the literature and finds strong evidence of heredity, often through more than one generation.

TABLE II

No. of Siblings	No. of Siblings Affected	Other Members Affected (History Only)
6	3	—
4	2	—
3	2	—
3	2	—
2	1	Mother of affected child

Symptomatology

Again I must stress that all my cases were asymptomatic. All optic fundi were examined and all were normal, even where the *x*-ray film showed gross digital marking. Intelligence was assessed by personal interview and where possible by a history of development, school performance, etc., from the mother; no mental retardation was found. This contrasts with the malignancy often ascribed to the condition as a result of selection. Nevertheless the condition is not wholly benign and possible symptoms must be discussed.

Papilloedema and Optic Atrophy may result if intracranial pressure rises, the optic atrophy being secondary to papilloedema. This forms an urgent, absolute indication for operation. From the literature it appears that this may occur at any age but generally before 5 years. The high incidences of this complication reported in the literature are a result of selection.

Mental Retardation.—On the face of it it seems unlikely that craniostenosis should cause mental retardation, and again one must allow for selection giving a false picture. Fletcher (1911) reviewed 87 cases and found all with normal intellect. Ingraham, Alexander, and Matson (1948), however, report a high incidence, 16 out of 50 cases being retarded. The literature generally refers little to this feature even though the most severely affected cases are reported. None of my 37 cases was retarded.

Treatment

Subtemporal decompression for increased intracranial tension was successfully used for many years, but linear craniectomy is more physiological; however, healing occurs rapidly, and to overcome this the bone end must be covered with polyethylene film (Ingraham, Matson, Alexander, 1948) or tantalum foil (Simmons and Peyton, 1947). Ingraham *et al.* report a "negligible mortality," the possible complications being haemorrhage and infection. The dura is left intact.

1. *Papilloedema and Optic Atrophy.*—Regression can be expected with operation. Visual defect may be improved or, at least, progress will be halted. There can be no doubt that this is an absolute indication for operation.

2. *Deformity.*—McLaurin and Matson (1952) report that operation in the first few weeks of life leads to normal or near normal skull contours. Later, results are "disappointing," and after two years no striking improvement can be expected.

3. *Mental Retardation.*—Ingraham, Alexander, and Matson (1948) report "improvement" in about half their cases operated on, the children remaining retarded. Their results are not documented well enough, and I would like to know whether due allowance is made for maturation and for subjective factors in the families who reported improvement. My view remains that mental retardation may be associated with, but not a result of, craniostenosis and that there is no adequate evidence that operation will benefit it. I do concede that where headache resulting from raised intracranial pressure has caused behaviour problems improvement will occur.

4. *"Releasing Growth Potential."*—In view of the foregoing and the fact that brain growth proceeds when skull growth is defective, I feel that in the absence of greatly increased intracranial pressure this somewhat nebulous indication for operation should be discounted.

Summary

Craniostenosis is a not uncommon hereditary disease affecting males predominantly, in which skull deformity

results from premature fusion of sutures of the cranial vault. It is of most significance when it occurs during the period of rapid brain growth. Although the condition has been recognized for a considerable time no review of an unselected series of cases has been reported.

A review of 37 cases shows the condition to be relatively common in Africans; the incidence and clinical features have been discussed, and it is concluded that the disease is much less malignant than hitherto thought. Only raised intracranial pressure leading to papilloedema or other consequent symptoms is regarded as an unequivocal indication for operation, but this complication must be remembered, particularly where multiple sutures are involved. The only other indication for operation is the correction of deformity, and this only in the first few weeks or months of life.

My thanks are due to Dr. H. C. Falcke, paediatrician, Coronation Hospital, for permission to publish the cases seen there; Professor R. A. Dart and Dr. P. V. Tobias for encouragement and facilities for photography; Mr. A. E. Wilkinson, Dr. F. P. S. le Roux, Mr. R. Klompfass, and Mr. A. Shewitz for the photographs; Sister H. Madigisa and Miss H. McLean for assistance in collecting and transporting cases for investigation; and Dr. R. Glyn Thomas for reviewing and discussing the *x*-ray films.

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The new Factories Act, 1959, makes it obligatory for an industrial first-aider to have prescribed qualifications. What these qualifications will be has not yet been laid down, but it is probable that regulations will shortly be made requiring first-aiders to hold a valid certificate of one of the ambulance associations. At present only six out of 10 industrial first-aiders hold valid Red Cross, St. John or St. Andrew certificates, according to a survey which details the first-aid provision in 244 companies with up to 1,000 employees. Of the firms examined 70% had all male first-aiders and only 10% all female, mostly in firms with a single first-aider. The number of first-aiders under 30 and over 60 is small, and the most common age is in the forties. Sixty per cent. of all first-aiders received their training from the St. John Ambulance Association, 10% from the Red Cross, and 5% from the St. Andrew Ambulance Association. More than half the firms questioned experience difficulty in recruiting first-aiders, but of these only 22 provide training facilities of any sort. In fact, three-quarters of the companies make no practical effort to help with training, although nearly half provide some type of incentive for a first-aider to become qualified. Sixty per cent. make no payment at all to first-aiders; among the other 40% annual payments range from 30s. to £40. (*First Aid in the Smaller Company*, Industrial Welfare Society.)

SERUM PROTEINS IN SYSTEMIC LUPUS ERYTHEMATOSUS

BY

E. G. REES, M.B., M.R.C.P.
Senior Registrar, Department of Pathology

AND

M. WILKINSON, M.D., M.R.C.P.
Medical Tutor

St. Bartholomew's Hospital Medical College, London

Of the diagnostic tests for systemic lupus erythematosus, the L.E. cell phenomenon, the differential agglutination, Coombs, Wassermann, and paratoluene sulphonic acid tests all depend upon protein abnormalities. Nevertheless, the serum proteins in systemic lupus erythematosus have received comparatively scant attention in the literature and little information is available regarding their diagnostic value.

There is general agreement that while the total serum protein level may be normal, the serum albumin is often reduced and hyperglobulinaemia is frequent. Unfortunately, reports of serum protein electrophoretic studies in systemic lupus erythematosus relate to small series of patients. Probably because of this and because some authors have failed to make comparisons between the absolute figures and those of normal controls, further findings are conflicting. Smith (1954) found an increased α_2-globulin in six patients with "little or no evidence of renal disease," and a reduced level in four patients with nephropathy. Baptista *et al.* (1956) and Reiner (1950) also found that the α_2-globulin level tended to be high, but Walker and Benditt (1950) and Sunderman and Sunderman (1957) report normal levels without mentioning their relationship to proteinuria. The β-globulin level has been reported to be normal (Reiner, 1950; Smith, 1954; Sunderman and Sunderman, 1957) or reduced (Walker and Benditt, 1950; Baptista *et al.*, 1956). All workers seem agreed that the α_1-globulin level is normal in systemic lupus erythematosus and that the γ-globulin is usually increased, though Baptista *et al.* (1956) are alone in finding the latter change less frequently than the increase in α_2-globulin.

The present study was undertaken to define the serum protein changes in systemic lupus erythematosus, to ascertain whether these changes could be of diagnostic or prognostic value, and to correlate the changes with disease activity and manifestations.

Materials and Methods

Total protein estimations and electrophoretic studies were done on 71 blood specimens from 31 patients with systemic lupus erythematosus. In every case the clinical picture was compatible with this diagnosis, which had been confirmed by the demonstration of the L.E. cell phenomenon.

The total protein estimations were made on serum, using the biuret method (Gornall *et al.*, 1944).

Electrophoretic studies were done on the same sera, using a technique similar to that described by Flynn and De Mayo (1951). 0.02 ml. of serum was applied to a 3-in. (7.5-cm.) wide strip of Whatman paper No. 1, and

the separation performed in a veronal buffer (*p*H 8.6) (ionic strength 0.05) for 16 hours. The applied potential was 2.5 volts/cm. length of strip. The strips were dried for 15 minutes at 100° C., stained for 10 minutes with light green (Gurr), and repeatedly rinsed in 2% acetic acid until a white background was obtained. After drying, the strips were rendered translucent by oiling (Grassmann *et al.*, 1951).

The scanning was done with an electrodensitometer (Laurence, 1954) and the absolute values of each protein fraction were calculated from the total protein result and the results of planimetry on the electrophoresis curves after extrapolating each segment of the curve to the baseline. No correction was made for differences in staining by the different protein fractions.

In order to provide a normal range of values, sera from 12 healthy young adults were similarly examined. These results are summarized in Table I.

TABLE I.—*Summary of Serum Protein Values (g./100 ml.) from 12 Healthy Young Adults*

	Total Proteins	Albumin	Globulin			
			α_1	α_2	β	γ
Mean	7·3	3·7	0·3	1·0	1·0	1·3
Standard deviations (S.D.)	0·38	0·39	0·1	0·16	0·19	0·25
Mean ± 2 S.D.	6·5–8·1	2·9–4·5	0·1–0·5	0·7–1·3	0·6–1·4	0·8–1·8

All statistical comparisons were made by using Student's "t" test.

Results

Untreated Systemic Lupus Erythematosus without Proteinuria

Two factors influencing the serum proteins in systemic lupus erythematosus are, firstly, the effect of the disease process, and, secondly, in those patients with nephropathy, the loss of protein in the urine. In order to get a clearer picture of the protein changes due to the disease process itself, serum protein results from 18 untreated patients without persistent proteinuria were analysed separately. The actual protein values are listed in Table II, but for convenience the results in these 18 patients are summarized in Fig. 1 for comparison with the healthy controls. The systemic lupus patients without proteinuria showed raised total proteins, low albumin, low α_2-globulin, low β-globulin, and markedly raised γ-globulin levels as compared with the healthy

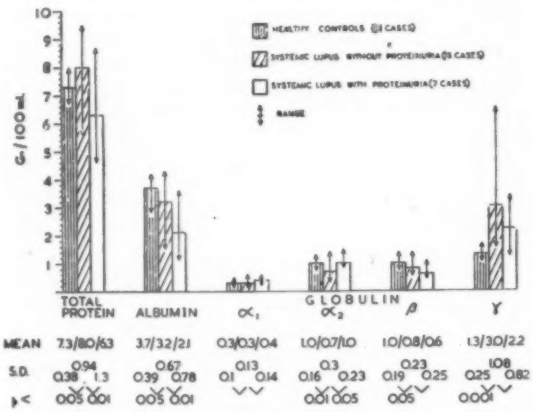
HEALTHY CONTROLS (II CASES)
SYSTEMIC LUPUS WITHOUT PROTEINURIA (18 CASES)
SYSTEMIC LUPUS WITH PROTEINURIA (7 CASES)
RANGE
G./100 ml.
TOTAL PROTEIN
ALBUMIN
GLOBULIN
MEAN 7·3/8·0/6·3 3·7/3·2/2·1 0·3/0·3/0·4 1·0/0·7/1·0 1·0/0·8/0·6 1·3/1·3/2·2
S.D. 0·38 0·94 1·3 0·39 0·67 0·78 0·1 0·13 0·14 0·16 0·3 0·23 0·19 0·23 0·25 0·25 1·08 0·82
p < 0·05 0·01 0·05 0·01 0·01 0·05 0·05 0·001

FIG. 1.—Serum protein results from 18 patients with systemic lupus erythematosus without proteinuria and from 7 patients with systemic lupus erythematosus and proteinuria, compared with those of 12 healthy controls. Statistical comparisons have been made between the patients without proteinuria and the healthy controls and between the patients with proteinuria and those without. Where a significant difference exists this is indicated in the bottom line.

controls. As can be seen from Fig. 1, all of these changes reached the 5% level of significance, but the elevation of the γ-globulin was much more significant.

There was no correlation between any of the initial clinical features and the serum protein changes.

The correlation between disease activity, as judged from the temperature, sedimentation rate, and clinical features was only fair, there being a tendency for the severely ill patients to have particularly low serum albumin and exceptionally high serum γ-globulin levels. Also in individual cases clinical improvement was usually accompanied by a return of the serum protein changes towards normal.

Though the changes in the whole group are of great interest, in practice, where one is concerned with an individual case, it is of more value to know the incidence of deviations from the normal range, which is taken as two standard deviations above and below the mean for the healthy controls and is shown in Table I. From Table II it will be seen that of the 18 patients with untreated systemic lupus erythematosus and without persistent proteinuria 5 had a serum albumin level below the normal limit, 10 had a low serum α_2-globulin, and only 2 had a low β-globulin level. A single patient had a serum α_2-globulin value above the upper normal limit, and, of much more interest, 17 of the 18 patients had a raised γ-globulin level. In only one patient were the serum albumin, α_2-globulin, β-globulin, and γ-globulin levels all ouside the normal limits.

TABLE II.—*Results of Initial Protein Estimations (g./100 ml.) on 25 Patients with Systemic Lupus Erythematosus Grouped as Follows:*

Patient	Total Proteins	Albumin	Globulin			
			α_1	α_2	β	γ
18 Untreated Patients without Persistent Proteinuria						
E. B.	8·7	3·1	0·4	1·4	1·0	2·8
G. D.	7·0	3·4	0·2	0·6	0·7	2·1
G. G.	7·7	3·5	0·3	0·9	0·7	2·2
P. G.	8·0	4·2	0·2	0·5	0·7	2·3
G. Gr.	8·8	3·7	0·1	0·4	1·0	3·6
J. G.	9·0	1·5	0·2	0·3	0·5	6·5
B. H.	8·4	3·8	0·3	0·7	0·8	2·8
R. J.	7·4	3·3	0·1	0·5	0·6	2·9
D. L.	7·3	3·1	0·4	0·4	0·8	2·5
J. L.	7·4	2·8	0·4	0·6	0·8	2·7
C. M.	9·0	2·5	0·3	1·2	0·9	4·1
S. M.	7·2	3·3	0·2	0·6	0·8	2·3
K. M.	9·2	3·9	0·3	0·6	0·6	3·9
H. R.	8·2	3·2	0·4	1·1	1·1	2·5
A. S.	5·6	2·9	0·3	0·4	0·5	1·5
E. S.	9·5	4·3	0·5	1·0	1·4	2·3
E. St.	8·0	2·4	0·6	0·7	0·7	3·7
P. S.	7·7	2·7	0·4	0·8	1·0	2·8
5 Untreated Patients with Persistent Proteinuria						
R. N.	5·4	1·5	0·2	0·8	0·4	2·6
E. O.	7·6	2·7	0·6	0·9	0·4	3·0
K. O.	4·6	1·1	0·4	1·0	0·8	1·3
Y. S.	6·0	1·7	0·4	0·8	0·5	2·6
J. W.	8·7	3·6	0·2	1·0	0·4	3·4
2 Patients Inadequately Controlled on Steroids and with Persistent Proteinuria						
J. Q.	5·5	1·7	0·5	1·5	0·7	1·2
E. T.	6·2	2·2	0·3	1·2	1·1	1·5

Effect of Proteinuria

The initial serum protein values of five untreated patients with persistent proteinuria, together with those of two patients already receiving small doses of steroid therapy and still showing clinically active disease, were

analysed separately (Fig. 1) to ascertain how the proteinuria modified the serum protein pattern. When the serum proteins of this group were compared with those of the 18 patients without persistent proteinuria, the following significant differences emerged (see Fig. 1). The total proteins and the serum albumin were even lower and the α_2-globulin was higher. The γ-globulin was lower, but this did not reach statistically significant levels. When compared with the healthy controls the serum α_2-globulin in the patients with proteinuria was normal but the γ-globulin was still significantly raised.

The absolute protein values for the seven patients with proteinuria are listed in Table II, and it will be noticed that six patients had a serum albumin below the lower normal limit, only one patient had a serum α_2-globulin slightly above the upper normal limit, four patients had a β-globulin below the normal lower limit, and only four had a γ-globulin above the upper normal limit. It was those patients with very heavy proteinuria who showed very low serum albumin and normal serum γ-globulin levels. Electrophoresis on a concentrated urine specimen from one of these patients showed that the urinary protein was mainly albumin, but there was also a little β-globulin and some γ-globulin (Fig. 2).

Effect of Therapy

In nine patients multiple protein estimations were made both before and during steroid therapy. In eight patients the serum albumin rose rather slowly towards normal, but in two of these patients, on whom frequent studies were made, normal values were reached only after 10 weeks' therapy, which was long after clinical suppression of the disease had been achieved. The α_2-globulin and β-globulin levels fluctuated but also tended to rise slowly during therapy. In all cases without proteinuria the γ-globulin fell within a few days, but only in two patients did it reach the upper normal range, and this occurred only after several months' therapy, during much of which time both patients had been in clinical remission. Fig. 3 shows the albumin and γ-globulin changes in one of these patients.

Similar trends were observed in five patients who were already on steroid therapy at the time of first testing and who had further tests.

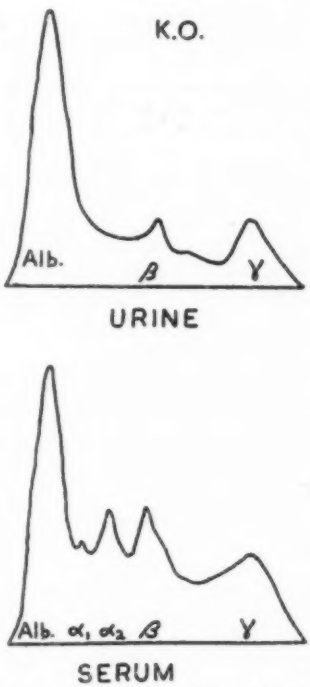

FIG. 2.—Tracings of electrophoretic patterns on serum and urine (concentrated 10×) from a patient with systemic lupus erythematosus and severe nephropathy. These tracings, which were not used in quantitative estimations, are somewhat distorted, as the sensitivity of the densitometer had to be increased to record the low protein concentrations.

Discussion

The almost constant change in the serum proteins in cases of systemic lupus erythematosus uncomplicated by proteinuria is a considerable increase in the γ-globulin fraction, and this is often accompanied by less constant and less marked but probably significant reductions in the serum albumin and α_2-globulin and β-globulin fractions. The large increase in the serum γ-globulin more than compensates for the reductions in the other components, so that the total protein value is normal or raised.

The cause of these changes is a matter for speculation. The increased γ-globulin is so constant as to suggest that it is a rather fundamental part of the disease process. It is known that this increased γ-globulin fraction contains many abnormal proteins, including those responsible for various positive serological reactions sometimes found in systemic lupus erythematosus. These include the L.E. cell phenomenon (Haserick et al., 1950), complement-fixation tests against human tissue antigens (Gajdusek, 1958), the Wassermann reaction (Coburn and Moore, 1943), and paratoluene sulphonic acid test (Wilkinson and Rees, 1958). Whether the Coombs and haemagglutinating factors in systemic lupus erythematosus are γ-globulins has yet to be demonstrated. Nevertheless, some of these reactions are probably antibody–antigen phenomena, and the raised serum γ-globulin is but the biochemical expression of a raised antibody level, much of which may be auto-antibody.

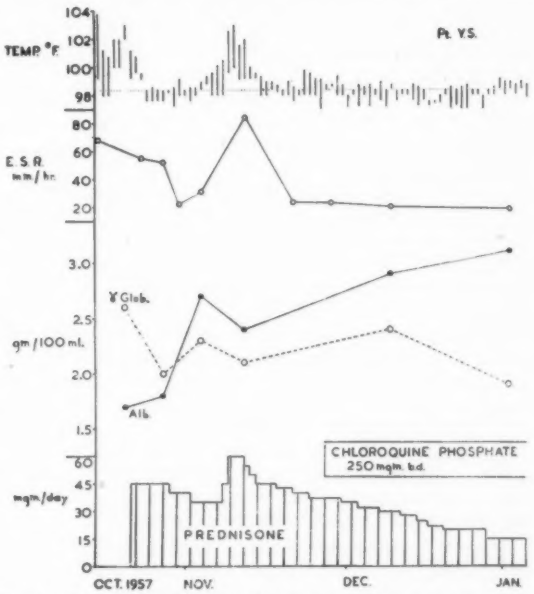

FIG. 3.—Serum albumin and γ-globulin levels from a patient with systemic lupus erythematosus correlated with temperature, sedimentation rate, and treatment.

The reduction in albumin, α_2-globulin, and β-globulin is much less constant and less marked, and may well be a non-specific result of a severe systemic illness with decreased protein anabolism, or increased protein katabolism.

When nephropathy supervenes the serum albumin falls further and the γ-globulin sometimes falls towards or into the normal range, presumably because of urinary loss, as was demonstrated in one of our patients. This urinary loss of γ-globulin undoubtedly includes L.E. factor, for this has been demonstrated in the urine (Korting and Schmitz, 1952), and we have noticed that in patients with proteinuria and a normal γ-globulin level the L.E. cells are demonstrable only with difficulty and in scanty numbers. On the other hand, the α_2-globulin rises to normal levels when proteinuria is present. This is found in the nephrotic syndrome whatever the aetiology, and presumably represents selective retention by the damaged kidney of the high molecular weight α_2-globulin.

It seems likely that the reason we have rarely found actual increases in the serum α_2-globulin, as has been reported by other workers, is because we have expressed the protein values in absolute figures and not as percentages, which in this instance, at least, would be misleading.

Even though the serum protein changes in systemic lupus erythematosus are not specific they have diagnostic value in a negative sense. This disease is most unlikely in a patient with a normal serum γ-globulin level in the absence of considerable proteinuria. Unfortunately, changes in the other protein fractions are too slight and too inconstant to be helpful.

In systemic lupus erythematosus the serum proteins probably have little prognostic value, for though those patients with a very low albumin and a normal or only slightly raised γ-globulin level did progress to an early death, this can be forecast from the invariable presence of severe nephropathy.

Summary

The total serum proteins and electrophoretic fractions were measured in a group of patients with systemic lupus erythematosus and compared with the results obtained from a healthy control group.

Eighteen untreated patients with systemic lupus erythematosus but without persistent proteinuria showed statistically significant increases in the total protein and γ-globulin levels and reductions in the albumin, α_2- and β-globulin levels that were probably significant. The raised γ-globulin was quantitatively the most striking change, and was above the upper normal limit in 17 of the 18 patients.

Seven patients with systemic lupus erythematosus and persistent proteinuria (five were untreated, two were on small doses of steroids) were compared with the 18 patients without proteinuria and showed significantly lower total protein and albumin levels and a higher α_2-globulin level. The γ-globulin level was lower, but not significantly so. The α_2-globulin level in the patients with proteinuria was not different from that of the healthy controls, but the γ-globulin was still significantly raised.

Therapeutically induced remissions were accompanied by a reversal of the serum protein changes towards normal, but it was exceptional for the γ-globulin actually to reach normal levels.

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TUBERCULOSIS IN THE FAMILY

BY

A. F. HUSTON, M.D., M.R.C.P., D.C.H.
Assistant Paediatrician, Kingston Group of Hospitals

AND

C. O. EDWARDS, M.B., M.R.C.P.
Assistant Chest Physician, Kingston, Surrey

From the Paediatric Department of the Kingston Hospital Group and the Kingston and Mortlake Chest Clinics

Recent years have seen a fall in the mortality and the incidence of all forms of tuberculosis in children and adults, and it is sometimes assumed that tuberculosis is becoming a relatively unimportant disease. The fall in tuberculous morbidity, however, is much slower than the fall in mortality, and tuberculosis remains among the most important of communicable diseases. In children the source of infection is now almost always an adult contact with pulmonary tuberculosis. The observations described here on tuberculous children and the adults in contact with them indicate the continuing significance of this aspect during a time when many changes are occurring in the management of tuberculosis and in the type of disease seen. The cases described were observed over a period of seven and a half years between 1951 and 1958. The district covered by the two chest clinics and the hospital group is primarily residential, and the overall incidence of tuberculosis is not unduly high. The type of tuberculous disease seen in 87 children under 14 who were treated in the paediatric department is shown in Table I. The disease was classified as primary or disseminated. *Primary* was taken to include mediastinal adenitis with or without segmental collapse, pleural effusion, cervical adenitis, abdominal adenitis, primary cutaneous lesions, and positive tuberculin tests in children under 4 years of age. *Disseminated* included meningitis, miliary tuberculosis, bone and joint disease, renal disease, and adult-type pulmonary disease.

TABLE I.—*Type of Tuberculous Disease in 87 Children*

Primary Disease (62 Cases)		Disseminated Disease (25 Cases)	
Bronchial adenitis only	27	Meningitis only	10
,, ,, with segmental collapse	11	,, with miliary	4
Pleural effusion	9	Miliary only	2
Cervical adenitis	7	Bone and joint	6
Abdominal ,,	3	Renal	1
Cutaneous	2	Adult-type pulmonary	2
Aged 3 and under with positive tuberculin test	3		

Tuberculosis in childhood may be diagnosed after the investigation of suspicious clinical symptoms or by examination of the child contacts of adult cases of tuberculosis in the chest clinic. The diagnosis in these 87 cases was made by the hospital clinician in 64 cases (39 primary and 25 disseminated) and at the chest clinic in 23 (all primary).

The clinical features of tuberculous disease in childhood are so varied as to cover the whole field of medical or surgical diagnosis among children. The principal features encountered are shown in Table II.

TABLE II.—*Clinical Features in 87 Tuberculous Children*

Vague ill-health	30	Other skin lesions	2
Loss of weight	10	Phlyctenular conjunctivitis	2
Pyrexia of uncertain origin	6	Abdominal pain	9
Irritability	12	Cervical adenitis	8
Drowsiness	9	Enlarged spleen	2
Convulsions	3	Limb pain	8
Neurological signs	4	Back ,,	3
Cough	15	Deformity	4
Chest pain	16	Limp	5
Signs in chest	12	Dysuria	2
Erythema nodosum	7	No symptoms	4

The early diagnosis of tuberculous meningitis provided the most urgent problems. Meningitis was present in 14 children while 19 others required lumbar puncture to exclude the diagnosis. There were other clinical features of note. Abdominal pain was a prominent feature in five children with primary intrathoracic disease, and in one an appendicectomy was performed. Enlargement of the spleen was not seen in miliary disease, but was noted in two small children who had large primary complexes. Chest pain and cough were more common than expected, although in general neither symptom was severe. Only four children were completely free from symptoms among the 23 diagnosed on contact examination at the chest clinic.

Tuberculin-testing

The clinical manifestations being so varied, it is generally agreed that tuberculin-testing plays an important part in the diagnosis of tuberculosis in childhood. All the children in this series had positive tuberculin tests. No convincing example of tuberculosis of any type with a persistently negative tuberculin test was found.

During the period 1955–8 tuberculin tests were performed on 920 children admitted to hospital and 69 (7.5%) were positive or doubtful positive. In 33 (48%) of these 69 and 3.5% of the total tested tuberculosis was diagnosed. Figures are unfortunately not available for the earlier period. The children tested were a sample of hospital in-patients selected by symptoms which might be caused by tuberculosis.

By comparison the incidence of positive tuberculin tests in local school-children of 13 prior to B.C.G. inoculation was 11% in 1954–5 and 7% in 1957–8. These figures are similar to the incidence of positive reactions of children in hospital with symptoms compatible with tuberculosis, but the hospital group was composed of much younger children, and nearly half the positive reactors required treatment for tuberculous disease.

Sources of Infection

A probable source of infection was found in 74 of children (Table III) and in 13 it was not known. Two possible adult sources of infection were present in nine instances, but only the most probable is shown in Table III. A likely source of infection was found

TABLE III.—*Sources of Tuberculous Infection in 74 Children*

	Father	Mother	Grand-parents	Uncles/ Aunts	Siblings	Others	Milk	Total
Probable infecting contact	20	9	10	8	2	10	—	59
Known sputum-positive	17	8	8	6	1	6	—	46
No. of children infected	26	10	11	9	2	10	6	74

in 85% of the children, and in 78% the disease appeared to be of human origin. Among the 13 children for whom no source could be found were five whose homes were in streets where tuberculous adults were known to live. Sources of human infection outside the family included a tuberculous landlady, dwellers in the same block of flats, and a greengrocer. No case of tuberculosis in a child could be traced to a school infection.

Milk-borne Disease.—During 1951–2 five cases of tuberculosis (two of cervical adenitis, two of abdominal adenitis, and one of spinal disease) occurred in children whose family milk supply had been from a local dairy, where heavy tuberculous infection had occurred. During 1954 a boy aged 5 developed abdominal adenitis after drinking tuberculous milk while on holiday.

Changes in the Management of Tuberculosis

During the period of observation many changes occurred in the management of tuberculous disease. Effective and prolonged chemotherapy, thoracic surgery, B.C.G. inoculation, the disappearance of sanatorium waiting-lists, and a more radical approach to the treatment of primary disease are factors which have played a part. The widespread use of isoniazid, an adequate number of beds for tuberculous adults, and B.C.G. inoculations are all factors which made their appearance between 1952 and 1954. That there has been a considerable change in the type of case seen in children and their contacts is shown in Table IV, in which the type of tuberculosis seen is compared with the estimated period of contact with the source of infection. A short period of contact was considered to have occurred when the adult source of infection had recent disease, or short or very intermittent contact with the child, while long-standing contact was considered to have occurred when the adult disease was severe or chronic, and the child lived in the same house or saw the adult repeatedly.

TABLE IV

		1951–4	1955–8
Children with primary disease		37	25
,, ,, disseminated disease		17	8
Contact—adult or milk	Short	10	19
	Long	34	11
	Unknown	10	3

The change in the character of the disease seen is further shown by the observation that 15 of the 25 children with primary tuberculosis in the period 1955–8 had mediastinal adenitis only, while of the 11 cases of long-standing contact 6 were due to sputum-positive tuberculous grandfathers.

In this latter period the incidence of adult cases with short contact with children was doubled and the incidence of disseminated disease in the children was

halved, while a source of infection could not be found in only three of the 33 children seen.

Diagnosis of the Adult Contacts

Most of the adult contacts were diagnosed in chest clinic practice, and the tuberculous children in the present series who were found on contact examination of these patients form only a proportion of the primary infections diagnosed in the chest clinic. In many other instances a family history of tuberculosis was found when children were admitted to hospital, although in a number of cases the information was not obtained without repeated questioning.

When no information could be gained from the family history of a child who appeared to have tuberculosis the family contacts were thoroughly investigated. It was usually found expedient to radiograph the suspect adults immediately after discussion of the child with the paediatrician. Seven previously unsuspected cases of tuberculosis in adults were revealed in this manner, five in the father, one in the mother, and one in an elder sister of 17. Six of these seven previously unsuspected cases of tuberculosis had tubercle bacilli in their sputum. Although few in number these adults were the source of an undue proportion of the most serious cases in children. Of their child contacts, one died of miliary tuberculosis, while two others were cases of tuberculous meningitis with disastrous permanent brain damage.

Four children died of tuberculosis. One, mentioned above, was a child of 18 months with extensive miliary disease affecting all organs. Another was a child of 12 months admitted to hospital with convulsions and hemiplegia. She was a contact of an elderly man with open pulmonary disease who lived in the flat above. The other two were both mongol mental defectives, aged 9 and 13, admitted to hospital with advanced meningitis and living only a few days.

Two other children, both under 3 years old, were left with permanent severe brain damage from meningitis. These two children, with the two mentioned above who were under 2 years of age, form 25% of the 16 children under 2 seen in this series.

Although the incidence of serious tuberculous disease in childhood and the contact of children with infectious tuberculous adults both show a substantial reduction over the past seven years, the need for continued vigilance is indicated by the cases seen during 1958.

Case Reports

Case 1.—A carpenter aged 41 failed to regain normal strength after "Asian 'flu" in November, 1957. He was referred for chest *x*-ray examination and found to have a large apical cavity on the day his 5-year-old daughter became unwell. His family doctor's alert appreciation of the possibility of tuberculosis led to the very early diagnosis of miliary and meningeal tuberculosis in the child, with complete recovery on treatment. His 9-year-old daughter was also treated for primary tuberculosis.

Case 2.—A 5-year-old child from Ireland developed tuberculosis cervical adenitis. No source could be found.

Case 3.—A boy of 12, examined as a contact, developed an apical focus. His grandfather, who lived in the same house, became unwell with cough and sputum, and was found to have open tuberculosis. The boy was virtually symptom-free and his lesion cleared with chemotherapy.

Case 4.—A 34-year-old engineer felt "run-down" for three months. Mass *x*-ray examination of his chest showed tuberculous cavities, and tubercle bacilli were found in his sputum. Both his sons were infected—one aged 8 had mild pleural pain and hilar adenitis, and the other, aged 5, had loss of weight, massive adenitis, and segmental collapse.

Case 5.—A girl of 12 developed a pleural effusion, and tubercle bacilli were isolated from the fluid. No source of infection was found in her large family or at her school. An elderly man with chronic fibroid phthisis and tubercle bacilli in his sputum lived in the same row of cottages, and the girl said she had often passed him as he was coughing.

Case 6.—A boy of 6 was admitted to hospital with general ill-health and a low-grade pyrexia. A tuberculin test was positive and he had hilar adenitis. No tuberculosis was found in his family, but an elderly man living in the flat above him had become unwell and was found to have pulmonary tuberculosis with tubercle bacilli in his sputum. The boy had often visited him.

*Case 7.**—A girl aged 18 months was admitted to hospital with convulsions and hemiplegia. A choroidal tubercle was seen in the fundus oculi. Tubercle bacilli were isolated from the cerebrospinal fluid. In spite of intensive treatment with streptomycin, isoniazid, P.A.S., and steroids she remained spastic, and developed optic atrophy and mental defect. In retrospect it seems that she did not recognize her parents for three days before admission, and had been unwell for two weeks. On *x*-ray examination of her family contacts, her father, a 41-year-old stoker, was found to have advanced bilateral cavitated tuberculous disease with tubercle bacilli in his sputum. He had a chronic cough. His brother and sister had had tuberculosis in the remote past, but he had never attended a chest clinic. He had been a prisoner of war in the Far East. Eighteen months after his return home in 1946 his 6-months-old son had died of meningitis, the infecting organism not being known. It seems probable that this infant had tuberculous meningitis. The tubercle bacilli isolated from this man's sputum and his daughter's cerebrospinal fluid were resistant to isoniazid, and only partially sensitive to streptomycin. As he had never received any previous treatment, it would appear that his infection was due in part to primarily drug-resistant organisms.

Thus, an account which is mainly of improved prognosis for tuberculous children and adults ends on the sinister notes of drug-resistant organisms and unsuspected infectious disease, the most pressing problems in the modern management of tuberculosis.

Discussion

In the observations described above there was rarely any conclusive evidence that any individual child was infected by a particular adult. Taken together, however, they indicate the importance of close contact with adult cases in the causation of tuberculosis in children, and are in accord with the observations in a much larger series in Sheffield in the period 1947–52 (Briggs *et al.*, 1955), when a human source was found in 81% of 401 cases of miliary, meningeal, or primary tuberculosis in children. They show, too, the particular dangers of the "sputum-positive" adult in the home, which was emphasized by van Zwanenberg (1955) in a survey of the contacts of 483 cases in Suffolk in 1949–53. Other observers, however, have found a lower incidence of contact with known cases. Half of a group of London school-children dying of tuberculosis between 1948 and 1952 had no history of tuberculous contact (Bentley *et al.*, 1954). In a tuberculin survey of East London school-children a source of infection was found in 41 out of 154 tuberculin-positive children, but in only 19 was the index case in the child's family

*This child has since died (of bronchopneumonia).

(Silver, 1958). In an earlier survey in Edmonton, in 1952–3, Davies (1955) observed that one or more known cases of tuberculosis resided in 65% of the streets of the borough, a condition in which infection of children outside their homes might be common.

When considering the relative influence of heredity and environment in the development of tuberculosis in 6,537 domiciliary contacts of 2,330 cases, Anderson *et al.* (1957) concluded that closeness of contact with the index case and the degree of infectivity of the case were the main factors in the development of tuberculous disease in children or adults living in the same house, irrespective of relationship. Whether children are infected by their relatives or by other adults, in their homes or elsewhere, would seem to depend mainly on the location of the infectious adult. The disappearance of sanatorium waiting-lists may well have been among the most important factors in the lowered incidence of tuberculous disease in children in recent years. In the mainly residential area of Surrey, where the patients in the above series lived, it is not surprising that the main source of infection should be within the home, while a number of children who appeared to have been infected from outside the home lived in blocks of flats.

It seems unlikely that there is anything exceptional in the observations we describe. They show, however, the value of co-operation between paediatrician and chest physician. For the paediatrician, tuberculosis remains one of the main clinical problems, a cause of morbidity and mortality as great as poliomyelitis, rheumatism or pyogenic infection, while tuberculin-testing of ill children appears to be an investigation of increasing value as the general level of tuberculous infection falls. For the chest physician, a tuberculous child is indicative of an infectious adult, occasionally of an undiscovered case. The danger to children of the open case of tuberculosis serves to emphasize the need to find and treat infectious disease, and to offer protection with B.C.G. to all children and adolescents likely to be in contact with tuberculous infection.

Summary

During the period 1951–8 a series of 87 tuberculous children were seen in the paediatric department of the Kingston Hospital Group: 62 had primary disease and 25 had various forms of disseminated disease.

A likely source of infection was traced in 74 of the 87 children. 68 appeared to have been infected by 59 tuberculous adults in contact with them—36 by parents, 22 by grandparents, uncles, aunts, and siblings, and 10 by adult contacts outside the family. Six children were probably infected by tuberculous milk. No source of infection was found in 13 cases.

Comparison of the periods 1951–4 and 1955–8 shows that the incidence of disseminated tuberculous disease in children fell from 17 to 8 cases; the incidence of prolonged contact between tuberculous adults and children fell from 34 to 11; and the incidence of an unknown source of infection in a child fell from 10 to 3 cases.

These observations emphasize the continuing need to regard tuberculosis as a serious problem, and to realize the danger to children of the tuberculous adult.

We thank Dr. A. A. Cunningham, consultant paediatrician, Kingston Hospital Group, and Dr. S. R. Wilson, consultant chest physician, Kingston Chest Clinic, for much help and advice; and Drs. A. Sakula and F. Connor Walker for access to records of adult contacts.

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USE OF HYDROXYDIONE IN PSYCHIATRY*

A CONTROLLED EXPERIMENT

BY

S. BENAIM, M.B., M.R.C.P., D.P.M.

Consultant Psychiatrist, Halliwick Hospital, London; formerly Senior Registrar, Bethlem Royal and Maudsley Hospitals

Ever since Bleckwenn (1930) and Horsley (1936) wrote on the use of intravenous barbiturates in psychiatric disorders, almost every new drug with narcotic or anaesthetic properties has been investigated by psychiatrists for the purpose of facilitating interviews, providing relaxation, reinforcing reassurance, uncovering repressed material, or promoting abreactions.

It was natural that, after the report on the anaesthetic properties of certain hormones by Selye (1941), these, too, should be investigated by psychiatrists. Selye (1942) stated that the most powerful anaesthetic actions are exhibited by steroids oxygenated at opposite ends of the molecule and having no double bonds in the rings. There was no correlation between hormonal and anaesthetic action.

Hydroxydione (21-hydroxypregnane-3,20-sodium hemisuccinate) is now widely used for its anaesthetic properties. Its empirical formula is $C_{25}H_{35}O_6Na$. This substance has no hormonal action and no salt-retaining properties in man unless given in very large doses. Its administration is safe, the LD_{50} being three times that of sodium thiopentone.

The action of the drug has been studied by Gordan *et al.* (1956), who report a decrease in cerebral blood flow, inhibition of oxygen uptake, and a decreased glucose uptake such as is found in pethidine and barbiturate anaesthesia. *In vitro* experiments were carried out by Elliott *et al.* (1957), and the effect of hydroxydione was compared with that of other anaesthetics. The findings of these and other authors suggest that the main action of the substance is on oxidative reactions, and especially on the inhibition of the entrance of glucose into the tricarboxylic acid cycle. Though Batt and Dally (1958) and O'Flanagan and McGuinness (1958) have written on the uses of hydroxydione in psychiatry, no controlled investigation has yet been carried out.

Experimental Method

It was decided that in order to assess the value of hydroxydione, it was necessary to compare its action

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with that of drugs whose use in psychiatric practice was well established. Amylobarbitone (" sodium amytal ") and methylamphetamine hydrochloride (" methedrine ") were chosen for this purpose.

Every patient in this study was to receive the three drugs, the sequence of administration being randomized. This measure was taken to control the fact that one drug may affect the response to the next drug administered. In our investigation each substance had the same chance of being first, second, or third.

Twenty patients were chosen among those who were thought likely to benefit from administration of the drug, tension and anxiety being symptoms present in all. The individual diagnostic categories were: depressive states in 8 patients, anxiety states in 6, hysterical reactions in 4, and schizophrenia in 2.

The procedure of administration was standardized by introducing a structured interview. In this a non-directive approach was used. The patient was asked to report and describe any changes in symptoms or any peculiar sensations he might experience during and after the injection, and to tell if and when he should become sleepy.

He was next encouraged to associate freely, and only at the end of the interview was he questioned about history and symptoms. All this information, together with the therapist's observations, was recorded on a special printed form.

On the day after the interview the patient was given a simple questionary on the effects of the drug: Did he like the injection? Was it pleasant? Would he care for another? Did he remember the interview? Did he experience any changes in symptoms? How long did such changes last?

On the basis of the information derived from the interview and questionary, we noted the effect of the drugs in respect of the following items: (1) improvement in affective contact during interview; (2) affective discharge during interview; (3) repressed material obtained during interview; (4) relief of tension and anxiety during interview; (5) depression or excitement following interview; (6) amnesia for interview; and (7) desire for further injection.

The excitatory effect of methylamphetamine and the depression which so often follows differ so greatly from the effects of the other two drugs that a detailed comparison seemed unnecessary, and the results are not included in this study. We proceeded, therefore, with a comparison between the effects of amylobarbitone sodium and hydroxydione.

Dosage and Technique of Administration

The drugs were used in the following dosage: *Amylobarbitone Sodium:* 0.25–0.5 g. dissolved in 10 ml. of sterile water and injected slowly until nystagmus and dysarthria could be demonstrated. *Hydroxydione:* 0.5–1 g. dissolved in 10 ml. of sterile saline at body temperature. The dosage depended on the build of the patient, our aim being to administer the smallest dose needed to produce sleep. Experience had shown us that such dose produced good relaxation throughout the interview.

Hydroxydione must be injected rapidly, using a wide-bore needle and avoiding paravenous leakage. This minimizes the risk of thrombophlebitis. The patient should then elevate his arm for 30 to 45 seconds and the site of the injection should not be pressed upon. The technique of administration for amylobarbitone sodium is too well known to be described here. In this communication we shall confine ourselves to a description of the findings following administration of hydroxydione.

Clinical and E.E.G. Findings During Interview

For two to three minutes the patient is conscious of little change other than slight feelings of tiredness. There are no abnormal findings on physical examination no tachycardia, and no alteration of respiration or blood pressure. Occasionally dilatation of the pupil has been observed during this stage. The patient may say, " I feel a little strange," or, " It's a state difficult to describe."

After this time the patient begins to feel sleepy, complains of a heavy sensation, nystagmus and dysarthria occur, and sleep eventually supervenes three to five minutes after the injection and lasts 15 to 20 minutes. It has been reported that it is possible to prevent the occurrence of sleep by continuous stimulation of the patient—that is, by engaging him in conversation. We have not found this always successful, and, moreover, we feel that sleep in this setting has an important psychological effect and that the therapist should interfere as little as possible in all stages of the interview.

Waking is a gradual process, and clinically is not unlike the recovery following termination of an insulin coma. Not infrequently a difficulty in speech which Batt and Dally (1958) have observed to resemble schizophrenic thought disorder has been encountered. We have studied this phenomenon on a number of occasions.

During a time when the E.E.G. still shows characteristic sleep spindles, the patient becomes gradually aware of his surroundings and can obey such simple commands as " Open your mouth," " Give me your hand." He seems, however, unable to speak, and this difficulty remains while the level of consciousness improves. After full recovery patients described this state well with remarks such as " I knew all the time what I wanted to say, but it just would not come," and " I opened my mouth and nothing seemed to come out of it." In the next stage the patient begins to speak and can answer simple questions, though, at first, thought blocking may occur. His answers to more complex questions are likely to be vague and off the point. Because of the above observations it was decided to carry out a full neurological examination during the period of awakening. We observed hyperreflexia, mild apraxia, astereognosis, and some evidence of right-left dissociation. With the return of full consciousness and the disappearance of sleep spindles in the E.E.G. these signs could no longer be elicited. The above findings suggest a gradual return of cortical function.

This pattern of awakening varied little from patient to patient, contrary to what has been observed with intravenous barbiturates and nitrous-oxide anaesthesia. We found, however, that hysterical patients often exhibited dissociated behaviour on wakening. One patient, a young Jamaican nurse who had shown gross hysterical symptoms following an unfortunate love affair, drew herself up on her bed and actually leapt towards the therapist to the accompaniment of wild cat-like noises. Another patient, a young Irish housewife, had to be restrained by a nurse and prevented from

falling from bed in a state of wild and uncontrolled excitement. That such episodes were not attributable to hydroxydione is proved by the fact that these patients behaved in a very similar manner when given methylamphetamine or barbiturates. We believe with other workers that such behaviour is unconsciously motivated and represents the acting out of fantasies or dreams, expressing aggression or eroticism in a "somnambulistic manner." There was no recollection of these episodes once full consciousness was re-established.

Biochemical Findings

Blood-sugar estimations carried out on a number of patients during and at intervals after the period of sleep showed no hypoglycaemia.

In view of the mood changes, and especially the mild but constant euphoria and the relief of depression encountered during the interview, it was decided to investigate the possibility of serotonin release by the drug.

We found no significant differences in the level of 5-hydroxy-indoleacetic acid in the 24-hour urine collections of patients previous and subsequent to the administration of hydroxydione (Table I). These are preliminary results and we intend to carry out further biochemical studies.

TABLE I.—*Urinary Excretion of 5-Hydroxy-indoleacetic Acid*

	Before Injection	After Injection
Patient 1	2·6 mg./24 hours	3·0 mg./24 hours
,, 2	4·3 ,,	4·4 ,,
,, 3	3·8 ,,	4·4 ,,
,, 4	2·0 ,,	1·5 ,,
,, 5	1·0 ,,	1·0 ,,

Toxic Effects

Five of our patients developed thrombophlebitis at the site of the injection. This caused some pain and discomfort to the patient but settled completely within 48 hours in each case. In one patient this complication was attributed to faulty injection technique. Two of the patients had received the less soluble preparation.

No other reactions were noted. There was no evidence of extrapyramidal rigidity in our cases.

It has been reported that hydroxydione potentiates the action of barbiturates and other drugs. This fact could be of importance in cases where repeated injections are carried out. In our investigation, however, since patients received only one injection it was not thought necessary to discontinue night sedation or tranquillizers where these were being administered.

Results

The results of our comparison between the action of hydroxydione and amylobarbitone sodium are set out in Table II.

Discussion

The use of hydroxydione in anaesthesia has been reported by Galley and Rooms (1956), Taylor and Shearer (1956), and other workers. This substance was found to be preferable to thiopentone as a basal anaesthetic in that there was absence of post-operative lethargy, fatigue, and sickness.

E.E.G. studies have been carried out by Boyan *et al.* (1956), Dent *et al.* (1956), and others. Bellville *et al.* (1956) carried out a blind comparison of the sleep

TABLE II.—*Effect of Hydroxydione and Amylobarbitone Sodium on a Group of 20 Patients*

	Amylobarbitone Sodium	Hydroxydione	Difference Between Proportions Responding	t	P
Improved affective contact during interview ..	10	13	0·15	0·9603	N.S.
Affective discharge	12	5	0·35	2·2407	0·05
Repressed material obtained ..	12	9	0·15	0·9505	N.S.
Relief of tension	12	15	0·15	1·037	,,
Depression or excitement following interview ..	13	2	0·55	3·5898	0·01
Amnesia for interview	12	4	0·4	2·5819	0·02
Desire for further injection ..	6	12	0·3	1·9322	0·05

patterns obtained with hydroxydione and various barbiturates. All these workers agree that the patterns obtained are essentially similar, though it is presumed that steroid anaesthetics act at a different site in the line of biological oxidation. Farson *et al.* (1946) dispute the use of the word "anaesthesia" as applied to the cortical suppression by steroids, even though clinical and E.E.G. patterns are similar to those encountered in other forms of anaesthesia.

Coirault *et al.* (1955) found the drug useful in the treatment of delirium tremens. They carried out many investigations, including E.E.G. studies, and suggest that hydroxydione may have a cortical action.

Batt and Dally (1958) injected the drug in a dose of 0.5 g. to psychiatric patients and claim that 75% were improved by one single injection and approximately 50% showed some degree of abreaction during the interview. They comment on the dramatic relief of agitation in depressed patients and of depression in cases not showing agitation. There was little noticeable effect in schizophrenic patients. They conclude their study by stating that the use of this drug represents a real advance in psychiatry, particularly on account of the fact that consciousness is not affected and that there is relief of tension and anxiety.

O'Flanagan and McGuinness (1958) found the drug useful in uncovering the psychodynamics of the illness, especially in patients with early repressed memories. They also report no effect in catatonic patients and state that the drug is inferior to other abreactive agents.

Munro and Knox (1958) found the drug useful in the treatment of dehydrated patients who were disturbed and difficult to nurse.

Our own investigation confirms the usefulness of hydroxydione in psychiatric interviews, especially because these can take place in full consciousness and are not followed by depression. Moreover, the patient seldom has amnesia for the interview. On account of these properties the drug is less likely than others to affect therapeutic relationships adversely. It is most useful in short-term psychotherapy of tense patients unable to talk freely or to discuss their problems in ordinary situations without developing anxiety. It is less effective than other drugs as an abreactive agent.

We are unable, however, to support in full the findings of Batt and Dally, since in this study only two of our patients showed any degree of lasting improvement after one single injection.

As in the case of the above reports, we have found the effect of the drug on schizophrenic patients, and especially on catatonics, insignificant.

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Summary

Hydroxydione is a steroid anaesthetic which, when injected intravenously, enables interviews to be conducted in a setting free from tension and anxiety and confers on the patient a feeling of well-being.

Biochemical investigations and electroencephalographic patterns are discussed.

In a controlled investigation on 20 patients the action of the drug was compared with that of amylobarbitone sodium.

The indications for the administration of this drug in psychiatric patients are discussed.

I thank Dr. Linford Rees for his help in the design of this experiment and for his constant encouragement. Dr. V. H. T. James, of St. Mary's Hospital, kindly carried out the estimations of 5-hydroxy-indoleacetic acid. Schering A.G. Berlin, through their subsidiary company, Pharmethicals (London) Ltd., generously provided us with supplies of "presuren" (hydroxydione).

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THE MANAGEMENT OF RECURRENT APHTHOUS STOMATITIS

BY

WILFRED SIRCUS, M.D., Ph.D., M.R.C.P.
M.R.C.P.Ed.

Physician, Gastro-Intestinal Unit, Western General Hospital, Edinburgh; Lecturer in Medicine, University of Edinburgh

In a previous study (Sircus *et al.*, 1957) attention was drawn to the remarkable diversity of therapeutic specifics offered over the past half-century for the cure of recurrent aphthous stomatitis. These included all the vitamins, vaccinations, oestrogens, androgens, sulphonamides, arsenic, chlortetracycline, and *x* rays. In that study 23 cases of the major form of the disease were each treated, using a single blind procedure, with consecutive courses of folic acid, nicotinamide, riboflavine, and "becosym" (vitamin-B complex), and not a single subject benefited from any of the drugs. Likewise, ethisterone failed to influence the disorder where it appeared to have a temporal relationship to the menses. Radiotherapy administered in a careful double-blind series also had no effect in 14 cases. Oral cortisone, 50 to 75 mg. daily, did not improve any of four subjects, but one with a severely affected mouth greatly benefited from 200 mg. daily for a week.

Farmer (1958) reported apparent improvement in a similar group of cases using aneurine hydrochloride and folic acid in combination, and similar improvement with delta-hydrocortisone, topical hydrocortisone, and vaccination, but the results were assessed by the "patient's reaction to the treatment," and he concluded that "the manner with which treatment is given is probably as important as the drug used."

However, Truelove and Morris-Owen (1958) treated 22 cases of the major form of the disease with the local application of hydrocortisone hemisuccinate (2.5 mg.) linguets and reported healing of the lesions within 48 hours. On a maintenance dose of two to four linguets daily, five cases remained completely free "for some months," and "most others" were affected only by sporadic non-ulcerative "sore spots."

The social and emotional association of this disorder has been emphasized (Sircus *et al.*, 1957) and attention drawn to the beneficial effects often seen as the result of suggestion alone. The present study extends the inquiry into the management of the disease, paying regard to this observation.

The Investigation

Thirteen consecutive subjects attending with the major form of the disease, in whom aphthous ulcers were present continuously or with not more than a few days' freedom, were placed on a double-blind treatment trial. Observations were continued for approximately 12 months in each case. One month after an initial consultation, at which were recorded the details of the history and findings on examination, each patient was given a sequence of treatment with lozenges of identical appearance and taste. These consisted of a dummy preparation without any active ingredients; an antibiotic, framycetin sulphate ("soframycin"), 10 mg.; and a combination of framycetin sulphate, 10 mg., and prednisolone, 1 mg. The sequence of the different lozenges was distributed for each patient in random fashion, using a previously arranged plan. The patients remained 28 days on each of the preparations, allowing the lozenges to dissolve in the mouth slowly six times daily. A careful diary of the date of onset and the progress of the mouth lesions was kept by each patient from the day of the original consultation and brought monthly to the clinic. Subsequently to completing the three-months double-blind trial, most of the patients also went on to 28 days' treatment with hydrocortisone hemisuccinate (2.5 mg.) linguets, six times daily, and a further month on quinalbarbitone sodium ¼ gr. (50 mg.) twice daily. This part of the trial was open. The code of therapy for the double-blind part of the trial was not opened until the completion of the full six months of the sequence.

The mean age of the 13 patients (9 females, 4 males) was 39 years (range 28–60). The disorder was familial in three instances.

Only four patients were considered to have a stable social background and to have normal and fully adjusted personalities. One other was a partial mental defective, two showed moderate schizoid features, and three had well-developed chronic tension states associated with exogenous stress. The remaining three had moderate to severe depression of endogenous type.

The effects of management (see Table) were classified as "curative" where ulcers were absent from the mouth throughout the period of administration of the agent,

Effects of Management

Phase of Trial	No. of Subjects	Effects Classification		
		Curative	Helpful	Valueless
28 days after consultation ..	13	3	3	7
28 ,, ,, on dummy lozenges	13	0	6	7
28 ,, ,, antibiotic ..	13	2	6	5
28 ,, ,, steroid + antibiotic (prednisolone) ..	13	6	3	4
28 days on steroid alone (hydrocortisone)	11	4	4	3
28 days on sedation alone (quinalbarbitone) ..	8	3	1	4

"helpful" where the frequency of new ulcers fell by 50% or more of the average for the three months prior to the trial, and "valueless" where the incidence of the ulcers was unchanged or fell by less than 50%.

Results

When, however, the results are grouped and analysed the following features emerge.

Three patients, all female, showed no response either to the consultation or to any form of treatment. Two of these were those subjects with the schizoid features, and the third was depressed.

Three patients, one male, responded only to steroids, as shown by a "curative" effect of both steroid and antibiotic combinations and of steroid alone, but with no response to antibiotic alone. The group had no common features of personality or social background.

Four patients, two of each sex, responded equally well to every phase of the trial, including the period on dummy lozenges. Of these, two had marked evidence of chronic anxiety. Three of the four had shown a "curative" response to the initial consultation.

The remaining three patients improved after the consultation, but subsequently relapsed and showed no response to any form of therapy.

It is of interest to examine briefly the background and behaviour of the individual cases, as follows:

Case 1.—Woman aged 44 years. Duration of ulcers, 40 years. Lesions continuously present for 10 years. Chronic exogenous tension. Mother-in-law sick and living with her. Strong familial incidence of ulcers. Effective measure: steroids reduced ulcer incidence from continuous crops to three isolated lesions a month.

Case 2.—Woman aged 28. Duration of ulcers 1 year and present continuously. Schizoid features. No stress. Effective measure: nil.

Case 3.—Man aged 33. Duration of ulcers, 10 years, in continuous crops. Partial mental defective. Smokes 60 cigarettes in a day. Effective measure: nil. Subsequent to trial the patient was persuaded to stop smoking and to remove dentures at night; the incidence of ulcers then fell from 15 in a month to three.

Case 4.—Woman aged 34. Duration of ulcers, three years. Averaged eight new ulcers each month. Familial. Normal personality and no stress. Effective measure: no ulcers for six months subsequent to initial consultation.

Case 5.—Woman aged 60. Duration of ulcers, 14 years and in continuous crops. Marked depression. Effective measure: steroids reduced new ulcers to one or two small lesions a month.

Case 6.—Woman aged 44. Duration of ulcers, four years, in continuous crops. Immature, obese, depressed. Invalid husband and financial stress. Effective measure: ulcers reduced to one isolated lesion a month subsequent to consultation. This result, however, coincided with patient taking up employment and relieving financial anxiety in family.

Case 7.—Woman aged 30. Duration of ulcers, eight months and continuous. Onset coincided with serious conflict with father. They live together in tense atmosphere without conversing. Depressed, immature, tense. Through first three phases of trial had average of 15 new ulcers a month, and then suddenly went into complete remission and in subsequent five months remained totally free. Situation with father was unchanged, but remission coincided with finding a boy friend. Was seldom home, and was apparently happy.

Case 8—Woman aged 46. Duration, 25 years of continuous ulcers. Tense and depressed. Worried by "low class" noisy neighbours. Effective measure: nil.

Case 9.—Woman aged 45. Duration, seven years of continuous ulcers. Father and husband chronic alcoholics. Mother-in-law living with her. Severe migraine. Effective measure: dramatic disappearance of ulcers soon after beginning trial, and remained clear of ulcers for nearly six months; but this effect coincided with her mother-in-law moving elsewhere and her husband's alcoholic excesses diminishing.

Case 10.—Man aged 29. Onset of ulcers one year before, coinciding with attack of proctocolitis. Normal personality and no stress. Effective measure: steroids.

Case 11.—Man aged 40. Duration of ulcers, 20 years. Three or four ulcers each week, lasting 21 days. Normal personality and no stress. Effective measure: all phases of treatment subsequent to consultation, and including dummy lozenges, reduced incidence to two ulcers a month of seven days' duration.

Case 12.—Woman aged 30. Duration of continuous ulcers, two years. Onset during pregnancy and immediately after the discovery of husband's infidelity. Since then, frigid, depressed; migraine. Home atmosphere very tense. Effective measure: has had only one ulcer in the six months subsequent to the initial consultation.

Case 13.—Man aged 52. Not more than one week free from ulcers in two years. Tense, worrying man. Frustrated by failure to buy available business employing him for last 20 years. Effective measure: all phases of treatment, including dummy lozenges, were effective. Had 10 ulcers in a month when, owing to secretarial error, he failed to receive a supply of lozenges. In subsequent four months had only two ulcers.

Comments

It is notable that 6 of the 13 patients showed a remarkable response to the initial consultation, and before any therapy had been instituted; three subsequently remained totally free from lesions during the nine-months follow-up. The other three relapsed after a month or two, and then proved resistant to all therapy, including hydrocortisone. Furthermore, dummy lozenges produced a reduction of over 50% in the frequency and duration of ulcers in 6 of the 13 subjects. Therapy for this remittent disorder must be set against this backcloth before judgment is made on its efficacy. Nevertheless, local application of a steroid, prednisolone or hydrocortisone, is capable in approximately a quarter of the subjects of bringing about a sustained remission from the disease where all other measures, including suggestion, appear to fail.

In the absence of any knowledge of the basic aetiology of recurrent aphthous ulceration, management must remain empirical and aimed at associated features which may be acting to effect continuity of the disease process. Thus the evidence from this and the previous study (Sircus *et al.*, 1957) suggests that the interest of the physician, sedation, and the resolving of social and emotional problems do more than any other procedures to effect control in those cases where chronic anxiety,

tension, or depression of exogenous origin is clearly evident. No such value has been shown where the abnormal states of mind appeared to be endogenous in nature. Where no such exogenous stress or endogenous abnormality is associated with the disease, then steroid therapy remains the most useful of the procedures examined. Two additional points of management may here be mentioned, though not a part of the main study.

Extremely severe and continuous ulceration of the mouth with multiple giant ulcers has been managed with bed rest and corticotrophin, 80–120 units intramuscularly daily, for five to seven days on three occasions, with complete resolution within 10 days in each case. Subsequent relapse after some months, however, has been the rule.

Infrequently occurring isolated ulcers have been most effectively controlled by instructing the patient at the first evidence of a new lesion, either the appearance of a vesicle or of a tiny painful break in the mucosa, to touch it with a small crystal of copper sulphate held in tweezers, after preliminary swabbing of the area with amethocaine solution. During the next 24 hours a lozenge of prednisolone or hydrocortisone is placed in the vicinity of the lesion every few hours and there allowed slowly to dissolve.

Unfortunately for the majority of the sufferers from the frequently recurrent or continuous form of the disease, relief must await further advances in our knowledge of the aetiology.

Summary

Thirteen cases of severe recurrent aphthous ulceration of the mouth were subjected to a double-blind trial to determine the value of antibiotics and steroids in management.

The trial was so designed that the influence of suggestion and the interest of the physician could be appreciated and evaluated.

It has been shown that antibiotics are of no value in treatment, and that steroid hormones have a useful but limited application. Suggestion and medical interest are shown to have important effects which must be allowed for in judging therapy in this disease.

I am indebted to Dr. J. J. Segall and Roussel Laboratories Ltd. for the preparation and free supply of the identical sets of lozenges used in the trial, and to Miss Gillian Tucker for skilful assistance in the organization of the double-blind part of the study. Several of the cases were referred to me by Dr. J. W. Galloway and Dr. W. J. Baird, of the periodontal diseases department of the Edinburgh Dental Hospital, from whom I had the greatest encouragement and co-operation.

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According to records of the American Medical Association, Dr. LINDSEY S. MCNEELY, who will be 99 on November 14, is the oldest practising physician in the United States. He was born in a log cabin in 1860 and had been in practice at Kirby, near Pittsburgh, for 69 years. The only 99-year-old doctor in Great Britain, Sir WILLIAM COATES, who was born in June, 1860, has retired.

Medical Memoranda

Blood Groups and Toxaemia of Pregnancy

The discovery that certain blood groups, especially those of the ABO system, may be associated with particular diseases is comparatively recent. In 1954 Pike and Dickins examined the frequencies of ABO groups in toxaemic and non-toxaemic women and showed that group O was significantly more frequent in toxaemic mothers than in the remainder. Further expansion of their figures, with some modification, by Dickins (1955) confirmed this. However, examination of a second series by Dickins, Richardson, Pike, and Fraser Roberts (1956) showed no significant difference between the ABO blood group frequencies in toxaemic and non-toxaemic mothers, and Pearson and Pinker (1956) also were unable to find any difference between the two groups.

In discussing some of the biometric problems involved in establishing associations between blood groups and diseases Fraser Roberts (1955) stresses the large number of cases required and the importance of adopting rigid and precisely defined criteria for including cases in a series so that it is possible to add further groups which are individually too small for analysis, and to compare results from different parts of the world.

In presenting this small series the need for comparison with former publications has been borne in mind, and it is perhaps of interest that previous series have come from areas in England near to each other.

From time to time, beginning with Dienst in 1905, it has been suggested that toxaemia of pregnancy is due to ABO incompatibility between foetus and mother, isoimmunization of the mother taking place because the red cells of the foetus bear an antigen which is absent from the mother. The published results have not convincingly supported this hypothesis: for example, Hurst, Taylor, and Wiener (1946) found a greater number of incompatible blood groups between infants and mothers in cases of toxaemia of pregnancy than in normal cases, although the difference was not significant. They also found that some mothers showed a significant rise in isoagglutinin titre and that these formed a greater proportion of the toxaemic group than the normal group, but the series were too small for any definite conclusions to be reached.

Dickins (1955) also found that predominance of group O in toxaemic mothers persisted when those who had hypertension were considered as a separate group, but this increase was present both in those in whom the hypertension was due to the toxaemia and in those in whom essential hypertension occurred during pregnancy. Maxwell and Maxwell (1955), investigating cases of essential hypertension, however, were unable to find any significant difference in the blood-group distribution. In this series hypertensive cases were also investigated as a distinct group, but it was not possible to separate from this group cases of essential hypertension.

MATERIAL

The ABO and D blood groups of mother and infants in 1,087 pregnancies were determined; these included 149 cases of toxaemia. Apart from eclampsia, the

TABLE I.—*Frequencies of ABO Groups in Present Series Compared with Findings of Previous Authors*

Series	Type of Cases	O	A	B	AB	Total
Present	Toxaemic	65 (43·6%)	67 (45%)	12 (8%)	5 (3·4%)	149
	Non-toxaemic	422 (45%)	417 (44·45%)	76 (8·1%)	23 (2·45%)	938
	Total	487 (44·8%)	484 (44·5%)	88 (8·1%)	28 (2·6%)	1,087
	Special non-toxaemic group	69 (46·3%)	61 (40·9%)	15 (10·1%)	4 (2·7%)	149
Dickins *et al.* (1956)	Toxaemic	343 (48·3%)	286 (40·3%)	59 (8·3%)	22 (3·1%)	710
	Non-toxaemic	2,164 (45·8%)	2,045 (43·3%)	382 (8·1%)	135 (2·9%)	4,726
	Total	2,507 (46%)	2,331 (43%)	441 (8·1%)	157 (2·9%)	5,436
Pearson and Pinker (1956)	Toxaemic	296 (43·9%)	298 (44·1%)	58 (8·6%)	23 (3·4%)	675
	Non-toxaemic	4,809 (46·2%)	4,150 (39·8%)	1,080 (10·4%)	372 (3·6%)	10,411
	Total	5,105 (46·04%)	4,448 (40·12%)	1,138 (10·26%)	395 (3·56%)	11,086
Discombe and Meyer (1952)	Pregnant women	4,578 (45·78%)	4,219 (42·19%)	890 (8·9%)	313 (3·13%)	10,000
Richardson (1954)	Pregnant women	4,579 (45·79%)	4,238 (42·38%)	866 (8·66%)	317 (3·17%)	10,000

diagnosis of toxaemia was made, as in other series, by the presence of at least two of the following after the 28th week of pregnancy: (1) a blood pressure of 140/90 or over; (2) clinical oedema; (3) albuminuria not due to infection.

The average age of the non-toxaemic group was 26 years, with a standard deviation of 6.4; the average age of the toxaemic group was 26.6 years, with a standard deviation of 7.9.

As expected, the toxaemic group contained a significantly larger number of primiparae than the normal group. In case this proved to be a factor of importance a special control group was selected by which the toxaemic group was completely matched. These controls were chosen immediately after the admission of each toxaemic case by taking the first normal patient admitted which matched the toxaemic one in age and parity.

The definition of a heterospecific pregnancy was accepted as that in which the red cells of the foetus bore an antigen which was absent from the mother.

The investigation of the rhesus types was limited by the supply of antiserum and confined to the standard anti-D test.

RESULTS

The frequencies of the ABO groups in the whole series and in the toxaemic and non-toxaemic groups are shown in Table I, where they are compared with the findings of previous authors. It will be seen that there is no significant difference between the distribution in the toxaemic and non-toxaemic groups, including the specially selected non-toxaemic group, or between the total distribution in the present series and in the series of Dickins *et al.* (1956), Discombe and Meyer (1952), and Richardson (1954), but the difference that Pearson and Pinker (1956) noticed between their series and others is still shown when the present series is considered.

The incidence of homospecific and heterospecific pregnancies in each group is given in Table II, which shows that there is no significant difference between the toxaemic group and the main non-toxaemic group or between the toxaemic group and the specially selected non-toxaemic group, the value for P in each case being greater than 0.3 and 0.1.

TABLE II.—*Incidence of Homospecific and Heterospecific Pregnancies*

Pregnancy	Total Non-toxaemic Cases	Special Non-toxaemic Group	Toxaemic Group
Homospecific	750	115	125
Heterospecific	188	34	24
Total	938	149	149

The distribution of maternal blood groups in the heterospecific pregnancies of each group is shown in Table III. It will be seen that there is no difference between the groups.

TABLE III.—*Distribution of Maternal Blood Groups in the Heterospecific Pregnancies*

Blood Group	Total Non-toxaemic Cases	Special Non-toxaemic Group	Toxaemic Group
O	141	27	19
Others	47	7	5

Of the 149 toxaemic cases 122 had hypertension. Of these, 56 (45.9%) belonged to group O, 56 (45.9%) to group A, 6 (4.9%) to group B, and 4 (3.3%) to group AB. Apart from the rather small number in group B, there is no difference between this hypertensive group and either the toxaemic or the non-toxaemic group.

As was to be expected, the single D grouping revealed no difference between toxaemic and non-toxaemic mothers.

CONCLUSIONS

The results failed to reveal a preponderance of blood group O either in toxaemic mothers or in those with hypertension. Heterospecific pregnancies were not commoner in toxaemic mothers. In fact, there is no evidence to show that toxaemia of pregnancy is related to ABO or D blood-group distribution.

I wish to thank members of my laboratory staff for their assistance in this work.

G. S. ANDREWS, M.D.,
St. Woolos Hospital, Newport, Mon.

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Reviews

HISTORY OF CARDIOLOGY

The Story of Heart Disease. The FitzPatrick Lectures for 1956 and 1957 Given Before the Royal College of Physicians of London. By Terence East, M.A., D.M.(Oxon.), F.R.C.P. (Pp. 148; illustrated. 30s.) London: William Dawson and Sons, Ltd. 1958.

It was Sir Winston Churchill who remarked in 1944, when addressing the Royal College of Physicians, that "the longer you can look back, the further you can look forward." Probably in no field is this more true than in the biological sciences. An understanding of their evolution in a historical sense at once provides a perspective and a background to knowledge which re-emphasizes current experience and lights the way to further endeavour.

In this monograph, composed of the FitzPatrick Lectures for 1956 and 1957, Dr. Terence East, a distinguished cardiologist, has selected for study the history of the development of our knowledge of diseases and disorders of the heart and circulation. Wisely, the author has chosen four cardiological topics of special interest to the practising doctor, each lecture being complete in itself. The first, and to many readers no doubt the most interesting, is devoted to the history of cardiac diagnosis. It is fascinating to read again of Floyer and his pulse-watch, passing on to the gradual clarification of the arrhythmias, largely at the hands of James Mackenzie and Thomas Lewis—a slow progression over the space of two centuries. Percussion never yielded much in cardiology. How dependent we still are on palpation and how helpful radiology has become! Auscultation, introduced by Laennec in 1819 and elaborated so successfully in recent years with instrumental aid, is now yielding a richer harvest than ever before. Technical methods are steadily developing and will continue to do so. The second lecture, on the study of morbid anatomy—congenital defects, valvular lesions, and so on—is the natural sequence to the author's account of the clinical approach. This is a valuable chapter illustrating the gradual appreciation of the necessity to interpret signs in terms of pathology. The next lecture, on the coronary circulation and its disorders, is of special interest nowadays when atherosclerosis demands so much time and attention. The fourth and final chapter is devoted to a brief account of the history of the therapeutics of heart disease.

This is a scholarly book of great interest, beautifully illustrated with reproductions of portraits of many of the great physicians of the past and enlivened here and there by original and apt quotations from their classic contributions to cardiology. To the thoughtful doctor this monograph will make a great appeal. It deserves to be widely known. Few clinical teachers should be without this book.

A. Rae Gilchrist.

MOULDS AND ASTHMA

Mould Fungi and Bronchial Asthma. A Mycological and Clinical Study. By P. J. van der Werff. Volume I. With a foreword by Professor Dr. Johanna Westerdijk. (Pp. 174+xiv; illustrated. 22.80 fl.) Leyden: H. E. Stenfert Kroese N.V. 1958.

This book is essentially concerned with fungal spores and their occurrence in the air as possible allergens. The first chapter of 27 pages is a brief but extensive historical review of the literature dealing with the influences of climate and environment on asthma and with mycological and clinical investigations in mould allergy. Before one can begin to study clinically the role of mould spores as allergens it is essential to know what types occur in the air, their relative abundance, their times of appearance and main prevalence in the air, and the effect on their growth of local conditions both outdoors and indoors. The author has succeeded in giving a full picture of present knowledge in this field.

The book contains a morphological classification of the fungi with over 60 very good photomicrographs. There are full details of media suitable for the growth of the different culturable mould spores and technical details concerned with their successful culture. The author rightly stresses the need for uniformity and precision of nomenclature and the use of techniques which stand up to critical analysis. The longest chapter, of 46 pages, is devoted to a survey of the studies of the mould-spore content of the outside air, mainly of the culturable moulds, although work done by the use of other techniques is also referred to. Two smaller chapters set out the studies of air-borne fungi and of the fungi found in dusts from houses, factories, and workshops. The considerable mycological studies of the author of the outdoor air, and especially of the indoor air of houses, workshops, and factories, in the Netherlands add to the value of the book. The literature is very carefully reviewed, there being over 500 references. Besides the author index, it would have been a convenience to have had a subject index, as many will use this as a valuable book of reference.

This excellent book is a mine of information, reads well, and can be thoroughly recommended to all those interested in the role of fungi in the aetiology of asthma; it is perhaps appropriate that it should have come from the Netherlands, the home of that pioneer in the subject, Storm van Leeuwen. The appearance of the second and third volumes will be awaited with interest.

D. A. Williams.

PROGRESS IN POLIOMYELITIS

Poliomyelitis. Papers and Discussions Presented at the Fourth International Poliomyelitis Conference. Compiled and edited for the International Poliomyelitis Congress. (Pp. 684+xviii; illustrated. 60s.) Philadelphia, Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co., Ltd. 1958.

This volume adds another vivid record of progress in poliomyelitis. The first conference held in 1948 was concerned chiefly with epidemiology, pathology, and treatment, and at the end of it we did not seem to be getting very far. By the time of the second conference in 1951, however, the theoretical prospects had completely changed through the discovery by Dr. Enders that poliomyelitis viruses can be grown in tissue culture. This at once brought active immunization into the realm of practical policy, and by the date of the third conference in 1954 the first trial of the Salk-type of vaccine was already under way. This dramatic story is continued in this record of the fourth congress, held at Geneva in 1957. Emphasis has naturally shifted to consideration of the possibility that paralytic poliomyelitis can be made to disappear from the world by an adequate vaccination programme. The Salk-type vaccine has already given good results, but some think

it will be later replaced by an oral live virus vaccine. The behaviour of E.C.H.O. viruses and of cultured mammalian cells assumes special importance. If the disease is to disappear, only the chronic cases will remain, so they receive special attention in the discussions reported.

These are wonderful volumes, and all credit is due to the National Foundation for Infantile Paralysis for the tireless support which has been given to the solution of a very difficult problem. Victory may almost be in sight, and the Foundation has already changed its name so as to turn its attention to other crippling diseases.

W. Ritchie Russell.

PARASITES IN CLINICAL MEDICINE

Parasitology (Protozoology and Helminthology) in Relation to Clinical Medicine. By K. D. Chatterjee, M.D.(Calcutta). (Pp. 185; illustrated. Rs. 12.50.) Calcutta, India: Distributed by S. Bhattacharyya and Co. 1957.

This is a small volume, addressed mainly to undergraduates, and the aim has been to present basic facts with which a medical student should be familiar. It is also hoped that it will serve as a book of reference on human parasitology and on methods of recognizing the various parasites. These aims are admirable enough to justify the publication; certainly without a basic knowledge of parasitology the practitioner in the tropics will misdiagnose many cases and be responsible for perpetuating morbidity and increasing mortality. A well-illustrated work of reference is also essential for checking the identity of parasites which are from time to time encountered and the details of which cannot be carried in the memory. It can fairly be said that the author's aims have been accomplished, but it cannot be held that this has been done for the first time, for there are other volumes in this field with similar aims and covering similar ground.

The contents have been very well systematized and divided up under numerous headings and subheadings, so that information is easy to find; indeed, it might be considered that the desire to include some information under every heading has been carried too far, and sections on therapy—the uglier word "therapeusis" is used—have been included. Unfortunately, these add nothing to the value of the work, for in general the drugs used are only listed and details of their administration are not given. The space which could be saved by omitting these useless sections could well be used to augment the information given on differentiation between the many conflicting parasites and structures which simulate them; there is, for example, no warning concerning the fact that macrophages are not uncommonly confused with *Entamoeba histolytica*, nor are there specific instructions regarding differentiation of these structures, yet confusion between them has been responsible for much trouble in the past. There are also some small inaccuracies—for example, microfilariae of *Onchocerca volvulus* are described as having a crook-shaped tail. There is here clearly some confusion with *Acanthocheilonema streptocerca*. These criticisms, however, are relatively minor and are not meant to detract from what is a very valuable publication. Indian diseases rightly receive specially prominent attention, and the book will be of especial value to students in south-eastern Asia.

A. W. Woodruff.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Child with a Handicap. A Team Approach to His Care and Guidance. Edited by Edgar E. Martmer, M.D. (Pp. 409 +xxiv; illustrated. 82s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

Complex, Archetype, Symbol, in the Psychology of C. G. Jung. By Jolande Jacobi. Translated from the German by Ralph Manheim. (Pp. 236+xii. 21s.) London: Routledge and Kegan Paul. 1959.

A History of the Maida Vale Hospital for Nervous Diseases. By Anthony Feiling, B.A., M.D., B.Ch.(Cantab.), F.R.C.P.(Lond.). With a foreword by Sir Ernest Gowers, G.C.B., G.B.E. (Pp. 63; illustrated. 15s.) London: Butterworth and Co. (Publishers) Ltd. 1958.

The Story of Evans Medical 1809-1959. (Pp. 72; illustrated.) London, Liverpool: Evans Medical Supplies Limited. 1959.

Hormone. Einführung in ihre Chemie und Biologie. By Dr. Oldřich Hanč. (Pp. 633+xi; illustrated. DM. 40.) Jena: VEB Gustav Fischer Verlag. 1959.

Connective Tissue, Thrombosis, and Atherosclerosis. Proceedings of a Conference held at Princeton, New Jersey, May 12–14, 1958. Edited by Irvine H. Page. (Pp. 316+x; illustrated. $9.50.) New York, London: Academic Press. 1959.

Compendio di Elettrocardiografia. By Vincenzo Masini. 2nd edition. (Pp. 474+xv; illustrated. L.4,500.) Rome: Il Pensiero Scientifico Editore. 1959.

A Guide-Book to Biochemistry. By Kenneth Harrison. (Pp. 150+viii. 17s. 6d.) London: Cambridge University Press. 1959.

Hypnosis. Fact and Fiction. By F. L. Marcuse. (Pp. 224. 3s. 6d.) Harmondsworth, Middlesex: Penguin Books Ltd. 1959.

The Kinetics of Cellular Proliferation. Edited by Frederick Stohlman, Jr., M.D. (Pp. 456+xiv; illustrated. $5.75.) New York, London: Grune and Stratton. 1959.

Speech Disorders. Origin, Semeology, Genetics. Reports Prepared for the 11th Congress of Logopedics and Phoniatrics, London, August 17-22, 1959. (Pp. 166. Sw.Fr. 20.) Basle, New York: S. Karger. 1959.

Klinik und Praxis der Urologie. Klinik, Indikation, Diagnostik, Operative und Instrumentelle Eingriffe, Nachbehandlung. By Professor Dr. Werner Staehler. Vol. 1. (Pp. 892+ xxi; illustrated. DM. 240.) Stuttgart: Georg Thieme Verlag. 1959.

Zum Krankheitsbild des Sogenannten Cardiospasmus (Achalasia Oesophagei). By Peter Christian Alnor, M.D. (Pp. 78+viii; illustrated. DM. 11.80.) Heidelberg: Dr. Alfred Huthig Verlag GMBH. 1959.

Diagnosis of Congenital Heart Disease. A Clinical and Technical Study by the Cardiologic Team of the Pediatric Clinic Karolinska Sjukhuset, Stockholm. Second edition. By Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe, and Bengt Jonsson. (Pp. 866+xiv; illustrated. £10 3s.) Chicago: The Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1959.

Office Gynecology. By J. P. Greenhill, B.S., M.D., F.A.C.S., F.I.C.S.(Hon.). Seventh edition. (Pp. 572; illustrated. 68s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1959.

A Textbook of Surgical Physiology. By R. Ainslie Jamieson, M.B., F.R.C.S.Ed., and Andrew W. Kay, M.D., Ch.M., F.R.C.S.Ed., F.R.F.P.S.G. (Pp. 623+vii; illustrated. 55s.) Edinburgh, London: E. and S. Livingstone Ltd. 1959.

Diseases of the Nose, Throat and Ear. A Handbook for Students and Practitioners. By I. Simson Hall, M.B., Ch.B., F.R.C.P.Ed., F.R.C.S.Ed. Seventh edition. (Pp. 467+xi; illustrated. 21s.) Edinburgh, London: E. and S. Livingstone Ltd. 1959.

Expéditions Françaises à l'Himalaya. Aspect Médical. By Jean Rivolier, with the collaboration of P. Biget, F. Florence, A. Lapras, and J. Oudot. (Pp. 229.) Paris: Hermann. 1959.

Vision Screening for Elementary Schools. The Orinda Study. By Henrik L. Blum, M.D., Henry B. Peters, M.A., O.D., and Jerome W. Bettman, M.D. (Pp. 146+x; illustrated. 28s.) Berkeley, Los Angeles: University of California Press. London: Cambridge University Press. 1959.

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CONSCIOUSNESS DURING SURGICAL OPERATIONS

Before the advent of curare and the other relaxants, it was possible with a fair degree of assurance to estimate the depth of anaesthesia in terms of reflex motor responses to painful stimuli. Reaction to a mild stimulus like a touch on the cornea or prick of the skin indicated a nearness to consciousness or "light" anaesthesia. Failure to respond to a powerful one like inhaling strong ether vapour or a pull on the peritoneum indicated a state near death or "deep" anaesthesia. The ability to observe and interpret the so-called signs of the anaesthesia was rightly regarded as one of the necessary skills of the anaesthetist.

Gradually the interpretation of these classical signs became increasingly difficult. The effect on the patient of complex mixtures of drugs—opiates, barbiturates, analgesics, and volatile anaesthetics, to say nothing of spinal or some other regional block—often left the anaesthetist guessing. Unexpected responses by the patient became commoner, as did the development of sudden emergencies needing perhaps vigorous pulmonary ventilation in order to tide over a temporary overdose of one or other of the drugs. Until the advent of the relaxants, the signs which formed the basis for estimating the depth of anaesthesia were those due to the progressive depression of the cerebrospinal motor reflexes as anaesthesia deepened towards death. The relaxants altered the situation by abolishing the patient's ability to respond, however active the sensory receptors and the synapses were. Overnight the classical signs of anaesthesia became almost useless as a means of estimating depth of anaesthesia. Indeed, the very word anaesthesia reverted to the original meaning for which it was chosen by Oliver Wendell Holmes, the absence of sensation, instead of a meaning which had been gradually attached to it over the last 100 years—the absence of sensation and the absence of movement.

The ability to abolish all motor responses to pain by the simple procedure of injecting a relaxant, and thereby to offer the surgeon a patient relaxed to the point of cadaveric state, inevitably led to the present widespread practice of administering very small doses of sedative and anaesthetic drugs, though sufficient, it is hoped, to abolish sensation. If these doses are misjudged, the patient is exposed to the possibility if not the likelihood of being awake during the surgical procedure and of remembering what was done during that time. By 1951 this possibility was aired by W. W. Mushin,[1] who, citing a case and advocating the administration of pethidine as a prophylactic, said: "I am inclined to believe that this occurrence may be more common than we think. It is clear that, with the present-day large doses of relaxant, little objective evidence is available for the anaesthetist to determine the presence or absence of unconsciousness. A patient who is motionless may be conscious but curarized, while one who kicks may be unconscious and acting reflexly."

Following his advocacy, the use of pethidine to supplement nitrous oxide became widespread. Later, as I. C. Geddes and T. C. Gray[2] recently pointed out, controlled respiration with hyperventilation of the lungs, a universal adjuvant to the relaxants, added its own quota of analgesia. Nevertheless, the possibility of consciousness in these circumstances remained, and now another case has been reported by T. D. Graff and O. C. Phillips.[3] Doubtless there have been others. Graff and Phillips's patient was conscious and suffered "extreme pain" during a perineal operation; nitrous oxide and intravenous lignocaine and succinylcholine were administered. The anaesthetist did not realize that his patient was awake during the "apparently uneventful anaesthetic" and it was not discovered until afterwards when she was able to reconstruct details of the operation and of the discussions that went on between those in the operating-theatre.

As anaesthesia stands at present there is clearly a need for some means of detecting the presence of consciousness in an unresponsive curarized patient. The results of electroencephalographic studies[4,5] during anaesthesia offer hope in this direction. Indeed J. F. Artusio[6] demonstrated that there is a well-defined E.E.G. level of activity in patients during light ether analgesia who, though nearly conscious and able to answer questions, are yet insensitive to pain during major surgery. Help, too, is coming from the related fields of physiology and pharmacology in which the secrets of consciousness are being uncovered. The reticular activating system seems to be the important mechanism responsible for

[1] Mushin, W. W., *Proc. roy. Soc. Med.*, 1951, **44**, 840.
[2] Geddes, I. C., and Gray, T. C., *Lancet*, 1959, **2**, 4.
[3] Graff, T. D., and Phillips, O. C., *J. Amer. med. Ass.*, 1959, **170**, 2069.
[4] Siker, E. S., *Brit. med. J.*, 1956, **2**, 1326.
[5] Galla, S. J., Rocco, A. G., and Vandam, L. D., *Anesthesiology*, 1958, **19**, 328.
[6] Artusio, J. F., *J. Amer. med. Ass.*, 1955, **157**, 33.

maintaining the cerebral cortex in a state of alertness and receptivity, and its proper functioning is almost certainly essential for consciousness. In an address published in the opening pages of the *Journal* this week Dr. W. Feldberg, F.R.S., admirably reviews the physiological basis of consciousness, and points out that anaesthetics produce unconsciousness largely by virtue of their predilection for the reticular system. A number of drugs, mostly derivatives of phenothiazine, like chlorpromazine and promethazine, appear to have, among many other actions, some specificity for this system. Further search may produce others capable of depressing consciousness but with far less effect on the rest of the central nervous system or on the body elsewhere than the conventional anaesthetic drugs now used.

The control of consciousness during modern anaesthesia deserves further study, and the detection of consciousness as an immediate practical problem needs to be well aired, otherwise the primary purpose of anaesthesia, relief of pain, may be defeated by too much striving towards such other and newer goals as extreme relaxation and the mitigation of the physiological disturbances of opening the thorax, the heart, and the cranial cavity. The time may come, if it is not now, when anaesthetists must decide whether the risk (perhaps not so small as imagined) of the patient being conscious during surgery does not outweigh the risk (perhaps not so great as imagined) of using such well-known anaesthetics as ether, trichloroethylene, and halothane, or hypnotic drugs such as the barbiturates or the phenothiazine derivatives. The patient's need to be unconscious of his surroundings and free of pain is paramount.

KEEP THE PLANETS CLEAN

Before it set out on its journey to the moon, we are told by the Russians, their "Lunik 2" rocket was sterilized. This was in accordance with recommendations made by the Committee on Contamination by Extraterrestrial Exploration (C.E.T.E.X.) set up by the International Council of Scientific Unions in 1958.[1] So far, so good, for we can be sure that the rocket really did hit the moon, since Professor A. C. B. Lovell tracked it with his radio-telescope at Jodrell Bank and confirmed that it was heading for that target. And, to those whose daily lives bring them in repeated contact with sterilization procedures, the decontamination of a space vehicle may seem a simple matter. But is it?

At the recent International Astronautical Congress in London, R. W. Davies and M. G. Comuntzis, of the California Institute of Technology, described[2] how they sought the answer to this question at the behest of the United States National Astronautics and Space Administration. They pointed out that C.E.T.E.X. had been content to recommend the sterilizing of space probes without, unfortunately, suggesting how it could be done. So it was time someone repaired this omission. "All known micro-organisms," they begin, "perish when subjected to dry steam at 160° C. for 20 minutes." But, they add, about 20% of the components of present space vehicles cannot withstand 160° C. So they recommend, as a general disinfectant, ethylene oxide gas (C_2H_4O), which has a small molecule and can therefore get into tiny interstices, as well as dissolve in substances like rubber, plastic, and oil. It is effective against viruses, which are more difficult than most organisms to kill by radiation. When mixed with enough carbon dioxide to remove its inflammability in air, ethylene oxide can be used to sterilize most parts of any space probe—but not all. Heat sterilization will deal with most of the remaining components, and radiation, such as gamma rays from radioactive cobalt, with others. Still, say Davies and Comuntzis, we have not sterilized the lot, but only about 95% of it.

So some of the sterilizing must be done at an earlier stage; screws and bolts can be dipped in disinfectant before being inserted, other components can be washed and scrubbed, dust particles can be removed, and so on. Finally, the space probe has to be set up on the "launching pad," and microbes will get at it once more. So these authors recommended encasing it in a metal shroud enclosing a disinfectant atmosphere, and this is to be left on until the vehicle is safely out into lifeless space—or so they assume, though there was a once popular theory about living spores being carried around the Universe on meteoric dust.

The upshot of all this investigation, Davies and Comuntzis assert, is that you can never expect to sterilize a space vehicle completely; all you can do is to reduce its chances of infecting its target to an acceptable figure. This chance could be brought down to one in a hundred, or one in a thousand, or, at a still greater cost in time and trouble, to one in a million; but it will never sink to absolute zero. The question, therefore, is not simply one of "to sterilize

[1] *Nature* (*Lond.*), 1959, **183**, 925.
[2] Davies, R. W., and Comuntzis, M. G., "The Sterilization of Space Vehicles to Prevent Extraterrestrial Contamination," read to 10th International Astronautical Congress, London, Sept., 1959.
[3] Lowell, P., *Mars as the Abode of Life*, London, 1909, p. 188.
[4] Sinton, W. M., *Sky and Telescope*, 1959, **18**, 252.
[5] Wells, H. G., *The War of the Worlds*, London, 1898.
[6] Davis, I., and Fulton, J. D., "The Reaction of Terrestrial Micro-organisms to Simulated Martian Conditions," read to 10th International Astronautical Congress, London, Sept., 1959.
[7] Schmidt-Nielsen, B., in *Biology of Deserts*, edited by Cloudsley-Thompson, J. L., Institute of Biology, London, 1954, p. 173.
[8] Gold, T., in *Vistas in Astronautics*, edited by Alperin, M., and Gregory, H., London, 1959, p. 261.
[9] Whipple, F. L., ibid., p. 267.

or not to sterilize," but of how much trouble is it worth going to on the particular occasion. In other words, how susceptible is your target planet to infection?

Mars immediately leaps to mind, for there has been so much talk about the mysterious blue-green areas whose behaviour suggests the presence of vegetation. They are semi-permanent in position but undergo detailed changes of outline from year to year. Some of them undergo a seasonal change to brown, though this happens usually in early summer, not in the Martian autumn. The so-called "canals" were believed by Percival Lowell[3] to be the work of intelligent beings, because of their unnatural straightness and geometrical pattern, but the balance of opinion nowadays is in favour of their straightness being an optical illusion caused by the eye straining to see details beyond the limit of visibility. And W. M. Sinton[4] has found three lines in the spectrum of these areas corresponding to the hydrogen–carbon bond, which is characteristic of organic matter. It would be a pity if the first human traveller to land on Mars found its indigenous life mixed up with terrestrial organisms already planted there by an unmanned probe, just as H. G. Wells's[5] imaginary Martian visitors spread their "red weed" over the earth. But even if Mars is a dead world there is, apparently, still a risk of contamination.

In another paper read at this year's International Astronautical Congress, Captain I. Davis and Colonel J. D. Fulton,[6] of the U.S. Air Force School of Aviation Medicine, described how they managed to grow two strains of earthly soil bacteria, one of them spore-bearing, in an imitation Martian environment within "Mars jars." These jars contained a floor of red sandstone lava, which gave a similar spectrum to that of the Martian "deserts," surmounted by an atmosphere of commercial nitrogen, and were cooled at night to a temperature far below freezing point. But, even if dead bacteria are landed on a planet, they would mislead future investigators looking for simple organic compounds which might give a clue to the problem of the origin of life. So Davies and Comuntzis recommend that "Martian probes" should have their chance of carrying even one bacterium across space reduced to one in a million; and the same, they say, should apply to "Venus probes," for we do not know what the surface of that planet is like because it is permanently obscured by clouds.

As to the moon, they think a reduction in the chance of infection to one in 10, or at most one in 100, should be enough, because of the unlikelihood of life existing there. But who knows? Astronomers have reported seeing small grey spots on certain crater floors, such as that of Eratosthenes, which darken as the sun climbs higher in the lunar sky. And as to the absence of water, B. Schmidt-Nielsen[7] has found that desert rodents, such as the kangaroo rat, imbibe no water at all, but manufacture it in their bodies, though admittedly by oxidizing the organic matter in the dry seeds that they eat. Could not organisms live inside the alleged dust layer on the lunar surface, in spite of the virtual vacuum above? Here again, astronomers cannot agree whether there is a dust layer at all. T. Gold[8] thinks there has been so much erosion by meteoric impacts and solar radiation that the dust in many places must lie a kilometre thick, though all but the top 30 metres would be impacted by pressure. F. L. Whipple,[9] on the other hand, thinks that "loose dust on the lunar surface is practically non-existent," for the effect of corpuscular radiation from the sun would be to cement the dust grains into a crunchy, semi-porous matrix. So nobody yet knows what to put into an experimental "Moon jar" in order to find out if earthly organisms can grow there in a vacuum.

The question of how, and how much, to sterilize a space vehicle is, in fact, so beset with doubts that, at an informal discussion on space medicine held during the International Astronautical Congress, several medical men were heard to agree that they would not spend a penny (or a cent, as the case may be) on any attempt at sterilization, especially as it should not be long now before human travellers land on other worlds. For you cannot decontaminate a man; he has too much symbiosis going on inside him.

TREATMENT OF IRON-DEFICIENCY ANAEMIA

In the management of patients with iron-deficiency anaemia the first and most important step is to determine whether there is a remediable cause of loss of iron or of defective absorption. Many women during the reproductive years are on the verge of iron deficiency, and can readily become anaemic as a result of increased loss of menstrual blood, repeated pregnancies, or defective diet. But when no such precipitating factors appear to exist, a careful search must be made for overt or occult blood loss, especially from the gastro-intestinal tract, for it is a disaster to improve an iron-deficiency anaemia by iron therapy while leaving an operable tumour to become inoperable.

It would be an unnecessary and, indeed, insupportable burden on the radiological and pathological services to seek full investigations on every patient with iron-deficiency anaemia; the disease is far too common and too often of simple and innocent origin to justify such measures. A clinical estimate, based on a carefully taken case history and adequate physical examination, should enable those patients whose anaemia can be treated without further investigation

to be separated from the smaller number who require fuller investigation. The essential criterion is that a reasonable cause for the development of iron deficiency should be apparent. If this is the case the anaemia can be treated at once and the recognized causative factors dealt with so far as possible. If no reasonable cause is apparent, a thorough search to reveal one becomes essential.

The treatment of iron deficiency itself is usually a simple matter, since oral iron nearly always effectively remedies the deficiency. Ferrous sulphate has for long been regarded as the most satisfactory and economical form in which iron may be prescribed, but the introduction in recent years of organic iron preparations such as ferrous gluconate, succinate, fumarate, and various chelated compounds has been followed by a series of clinical trials concerned with the relative efficiency and freedom from side-effects of these oral preparations. O'Sullivan and colleagues[1] found little difference in the effectiveness of ferrous sulphate, succinate, or gluconate when given in a dosage providing 210 mg. of metallic iron daily. Ferric hydroxide in similar dosage proved unsatisfactory. They encountered gastro-intestinal intolerance in 3 of 23 patients taking ferrous sulphate, in 1 of 25 taking ferrous gluconate, and in 1 of 25 taking ferrous succinate. Among the 89 patients originally included in this trial 7 were completely refractory to all forms of oral iron given, but responded to parenteral iron.

As to intolerance, it seems probable that this varies directly with the dose of iron administered, and when ferrous sulphate is given in the low but adequate dosage of 0.4 to 0.6 g. daily side-effects are likely to be very uncommon. W. Brumfitt,[2] in a comparison of the therapeutic efficacy of ferrous sulphate and gluconate in uncomplicated iron-deficiency anaemia, gave daily doses of each compound containing 149 mg. of iron, roughly equivalent to two standard tablets of ferrous sulphate and four of ferrous gluconate. The haematological responses showed no significant differences and none of the 30 patients included in the trial showed intolerance of either drug. A further 50 patients treated with ferrous sulphate in similar dosage all responded satisfactorily to treatment, and none showed symptoms of intolerance. Apart from the relation of dose rate to side-effects during administration of iron, some patients, especially pregnant women, undoubtedly feel a strong aversion to green ferrous sulphate tablets. Thus, while N. Benstead and G. W. Theobald[3] found intolerance in 30 to 40% of pregnant women, and P. B. B. Gatenby and E. W. Lillie[4] in as many as 50%, W. Edgar and H. M. Rice[5] found intolerance in only 8 of 179 patients given white tablets containing the same quantity of ferrous sulphate as the familiar green ones issued normally at antenatal clinics. The study of D. N. S. Kerr and Sir Stanley Davidson[6] makes the assessment of real intolerance to different iron preparations even more difficult, since unrecognized control pills used in a double blind trial were found to cause the same incidence of side-effects as did pills containing iron compounds, including ferrous sulphate. It seems reasonable to conclude that, when minimal effective doses of any of these iron preparations are used, and any suggestion of the possible occurrence of gastro-intestinal symptoms carefully avoided, intolerance is likely to be uncommon. The choice between them must then be dictated by other considerations.

In this number of the *Journal* Drs. H. T. Swan and G. H. Jowett describe at p. 782 a statistically accurate method for assessing the efficacy of treatment which takes into account the changing rates at which haemoglobin rises during different phases of treatment and from different original haemoglobin levels. They show that ferrous fumarate is a satisfactory oral agent, having the advantage of disintegrating rapidly in the mouth so that it can be given to patients unable to swallow tablets, and having a low incidence of side-effects. They have not compared the therapeutic efficiency of ferrous fumarate with that of other organic compounds or of ferrous sulphate, but their statistical method seems well designed to allow valid comparisons of this sort to be made.

For the present, since there appears little to choose between these various compounds in terms of effectiveness, economic considerations suggest that ferrous sulphate, in a daily dosage of 0.4 to 0.6 g. daily, should still be the first one to try, since ferrous fumarate costs about five times as much and ferrous gluconate and succinate about seven times as much in equivalent doses with regard to the content of elemental iron. The chelated compounds are probably no more effective or non-toxic when used in equivalent dosage[7] and are still more expensive, but both they and the organic salts might reasonably be considered for use in the small proportion of patients who are clearly intolerant to ferrous sulphate. Whether organic salts or iron-chelates have a special place in the treatment of some complicated iron-deficiency states, as after gastro-intestinal operations, is still an open question.

[1] O'Sullivan, D. J., Higgins, P. G., and Wilkinson, J. F., *Lancet*, 1955, **2**, 482.
[2] Brumfitt, W., *Brit. med. J.*, 1959, **2**, 473.
[3] Benstead, N., and Theobald, G. W., ibid., 1952, **1**, 407.
[4] Gatenby, P. B. B., and Lillie, E. W., *Lancet*, 1955, **1**, 740.
[5] Edgar, W., and Rice, H. M., ibid., 1956, **1**, 599.
[6] Kerr, D. N. S., and Davidson, S., ibid., 1958, **2**, 489.
[7] Herridge, C. F., *Brit. med. J.*, 1958, **2**, 140.

TROUBLES WITH PYRIDOXINE

A deficiency of vitamin B_6 (which consists of pyridoxine, pyridoxamine, and pyridoxal) in the diet of animals causes delayed growth, anaemia, defects in amino-acid metabolism, and convulsions.[1] Deficiency of this vitamin in the diet of human babies was first reported from the U.S.A. Between 1952 and 1953 there was a small outbreak of convulsions in young infants who had been fed on cow's milk which had been modified to make it something like human milk.[2–6] These infants' daily intake of vitamin B_6 was less than 0.1 mg. The convulsions quickly and permanently ceased when pyridoxine was given or when the babies received milk of normal composition. Subsequently the infants developed normally.

Pyridoxal phosphate serves as a coenzyme in many systems, particularly decarboxylation, transamination,

deamination, and desulphydration. Animals receiving insufficient vitamin B_6 excrete in the urine more xanthurenic acid than usual; this is an abnormal product of tryptophan metabolism. The American infants lacking vitamin B_6 were found to excrete excessive amounts of xanthurenic acid after an oral dose of tryptophan. Using this test, O. A. Bessey and his colleagues[6] showed that clinical manifestations of deficiency, such as convulsions, may appear if the daily intake of vitamin B_6 falls below 0.1 mg., that the optimum intake is probably 0.2 to 0.3 mg. a day, and that an abnormal response to tryptophan is found before the development of clinical signs, so that it is a more sensitive index of deficiency.

While the discovery that deficiency of vitamin B_6 produces similar effects in human infants to those previously recognized in animals is of some importance, the circumstances were so unusual that such "pyridoxine-deficient" convulsions are unlikely to occur again. But cases have been reported of convulsions in infants who did not lack vitamin B_6 and in whom tryptophan tests were negative, yet whose convulsions were abolished by pyridoxine. "Pyridoxine-dependent" convulsions of this nature have been described by A. D. Hunt and co-workers[7] and O. A. Bessey and co-workers[6] from the U.S.A. and by A. Hennequet and co-workers[8] from France. None have yet been reported in Great Britain.

The convulsions in these cases appeared within a few hours or days of birth, whereas in the pyridoxine-deficient cases some months elapsed before the deficiency became clinically obvious. The affected infants in both groups also showed a characteristic irritability and gross motor overactivity. Exaggerated sensitivity to noise or handling, and rapid movements of the eyeballs and fluttering of the eyelids, have been stressed.[7 8] The electroencephalograph showed gross, though not specific, abnormalities, which were abolished within a few minutes by an intravenous dose of pyridoxine. The convulsions were uninfluenced by the usual anti-convulsants such as chloral hydrate, barbiturates, and hydantoins, but completely abolished by pyridoxine. These infants did not show any other signs of deficiency of vitamin B_6, and they required a daily dosage of pyridoxine varying from 2 to 5 mg. to prevent convulsions, a dose much larger than the physiological requirements. Withdrawal of the pyridoxine always resulted in a return of the abnormal behaviour and of the seizures, the time varying from two to five days.[7 8] Some of the infants with pyridoxine-dependent convulsions have also shown gross retardation of development, which, unlike their seizures, was not influenced by pyridoxine.

It seems likely that this is yet another inborn error of metabolism in which there is a single deficiency in enzyme activity. The chemistry of it is probably complex.[9 10] L. Sokoloff and his colleagues[11] have recently studied the cerebral blood flow, oxygen consumption, and respiratory quotient in the first reported pyridoxine-dependent child.[7] They found that consumption of cerebral oxygen was decreased during her seizures. This is the opposite of what is found in most types of convulsions, though decreased consumption of oxygen is also a feature of insulin hypoglycaemia, which is another example of a deficiency of a substrate essential to the brain.

Pyridoxine dependency is therefore worth considering as a possible cause of convulsions in any newborn or young infant whose seizures cannot be attributed to an adequate cause such as intracranial bleeding or hypocalcaemia, and which show no response to the common anticonvulsants. Proof of the diagnosis is dramatic cessation of the convulsions on treatment with pyridoxine; in addition, the grossly disturbed electro-encephalograph returns to normal almost immediately.

CONVALESCENCE

Few patients at the conclusion of treatment in hospital are fit and ready to go straight back to their tractors, offices, or kitchen sinks. They need a breathing-space; for the body has to repair the damage wrought by illness or surgery, and its organs to compensate for any loss of function; the mind has to assimilate what may well have been the most upsetting experience of a lifetime; and the spirit has to be renewed before the individual can plunge back into the business of living with zest. Hence the need for convalescent establishments. There the patient may spend a peaceful recuperative holiday. But is merely lying fallow for a fortnight enough?

For patients doomed by physical or mental incapacity to be for ever dependent on wife, husband, or daughter an occasional change of milieu is not only beneficial but essential if life is to retain any savour for those concerned. If the cripple can be accommodated for a few weeks in the appropriate holiday home, not only is he subjected to fresh stimuli from his new surroundings but his guardians are granted respite from their unending responsibility and are free for a while to renew contact with friends and relations in distant parts of the kingdom. Such a holiday is something to look forward to, and to be remembered and talked about afterwards. It can sweeten a marriage of sickness and health.

For the past three years a Working Party (chairman, Dr. N. M. Goodman) of the Ministry of Health has been examining the existing facilities for convalescence open to patients in the Metropolitan area, and it has just published its report.[1] It states, "The treatment of convalescence has remained a medical and nursing backwater. . . . It needs to become more active, more planned, and more integrated with other aspects and disciplines of medicine." It recommends that regional

[1] Bicknell, F., and Prescott, F., *The Vitamins in Medicine*, 1942, London.
[2] Snyderman, S. E., Holt, L. E., jr., Carretero, R., and Jacobs, K. G., *J. clin. Nutr.*, 1953, **1**, 200.
[3] Molony, C. J., and Parmelee, A. H., *J. Amer. med. Ass.*, 1954, **154**, 405.
[4] Coursin, D. B., ibid., 1954, **154**, 406.
[5] —— *Amer. J. Dis. Child.*, 1955, **90**, 344.
[6] Bessey, O. A., Adam, D. J. D., and Hansen, A. E., *Pediatrics*, 1957, **20**, 33.
[7] Hunt, A. D., Stokes, J., jr., McCrory, W. W., and Stroud, H. H., ibid., 1954, **13**, 140.
[8] Hennequet, A., Lyon, G., Debris, P., and Le Balle, J. C., *Ann. Pediat.*, 1959, **192**, 197.
[9] Killam, K. F., and Bain, J. A., *J. Pharmacol. exp. Ther.*, 1957, **119**, 255.
[10] —— ibid., 1957, **119**, 263.
[11] Sokoloff, L., Lassen, N. A., McKhann, G. M., Tower, D. B., and Albers, W., *Nature (Lond.)*, 1959, **183**, 751.

[1] *Convalescent Treatment*, Ministry of Health, London. H.M.S.O. 3s.
[2] *Brit. med. J.*, 1951, **2**, 347.
[3] Day, G., ibid., 1959, **1**, 1178.

hospital boards should regrade convalescent facilities into establishments where active treatment is given (to be known as "convalescent hospitals") and homes which can offer only the "recuperative holiday type of care." The latter should no longer be the responsibility of the hospital service but of local authorities. Convalescent hospitals, the report goes on, should be upgraded where necessary, and a more vigorous policy undertaken for rehabilitation of the sick on lines similar to those developed for rehabilitation of the disabled.

There is indeed great need for overhaul, and has been for a long time.[2] It is common practice, the report observes, for hospitals to send patients for two weeks' convalescence, and at the end of two weeks they are apt to be discharged willy-nilly. And during that fortnight who really is responsible for them? The consultant who formerly had charge and is now some score of miles away? Or the unbriefed doctor who smiles encouragingly on his rounds? It is often a time of groundless fears, doubts, and uncertainties for the patient, and there may seem to be no one to whom he can turn for counsel. He is not allowed to leave the home believing wholeheartedly that he is as well as he feels; he is not allowed to cease being a patient, for, as G. Day[3] has recently said, looming ahead is that ominous visit to the consultant's follow-up clinic. Too often the patient finds his family practitioner completely in the dark about what has been happening to him. The doctor does not know how much the patient should do, or with what treatment, if any, he should persevere; he too has to wait until after the out-patient appointment, which may be weeks later. Meanwhile the patient is debarred from returning to work, productive employment is lost to the country, and the national insurance coffers are further depleted.

This is a shrewd report, and timely, because medicine and surgery are increasingly effective in ridding the patient of his physical handicap and getting him back on the road. Sometimes this is rather like performing highly skilled running repairs on the car, when really it may be the driver who needs attention, for he is shaken and dispirited, and craves the restoration of his self-confidence.

NOBEL PRIZE

Two American biochemists are sharing the Nobel prize in physiology and medicine awarded this year. They are Professor Severo Ochoa, who left Spain to settle in the U.S.A. and is now at the New York College of Medicine, and Professor Arthur Kornberg, who is professor of biochemistry at Stanford University, California. The value of the prize is £15,219.

These two distinguished biochemists have worked on the artificial synthesis of nucleic acids by means of enzymes. The nucleic acids in the cells are generally believed to transmit genetic information, which is thought to be laid down in the nucleic-acid molecule as a code based on permutations in the order of four characteristic bases. A knowledge of the mechanism of synthesis of such a molecule, which contains within itself the key to the vital processes of the cell, is thus of the greatest importance.

In 1955 Professor Ochoa and his collaborators announced the discovery in extracts of *Azotobacter vinedandii* of an enzyme, called by them polynucleotide phosphorylase, which would catalyse the formation of highly polymerized polyribonucleotides from 5′-nucleoside diphosphates. It thus became possible for the first time to achieve the synthesis of ribonucleic acid (R.N.A.) *in vitro* in the absence of living matter. A comparable advance in a closely related field was made in 1956 by Professor Kornberg and his associates, who found an enzyme in extracts of *Escherichia coli* which would polymerize deoxynucleoside triphosphates to form deoxyribonucleic acid (D.N.A.).

ROYAL MEDICAL BENEVOLENT FUND

A deficit of nearly £4,000 in the annual accounts of the R.M.B.F. emphasizes its need for more donations. Despite the beginning of Health Service pensions last year, the number of new applications for charitable assistance increased by twenty over the previous year, according to the Fund's annual report presented at the annual general meeting by the honorary secretary, Dr. T. Anwyl-Davies. Members of the medical profession who contribute to the Fund may be assured that their money will be spent wisely and will bring seriously needed relief to their less fortunate colleagues. For the Fund sets out to help "all distressed and deserving members of the medical profession, their wives, widows, and children. All are treated impartially, and urgent cases are helped immediately." At the meeting Sir Henry Tidy, the President of the Fund, drew attention to the very large contribution of £11,000 from the Medical Insurance Agency. But the M.I.A., he said, also had other claims on its balances to consider, and consequently the Fund should aim at increasing its other sources of income. Individual subscriptions from doctors are as badly needed as ever, and should be sent to the Fund at 37, St. George's Road, Wimbledon, London, S.W.19.

B.M.A. IN CATHEDRAL CITIES

Three of our loveliest cathedral cities have in the same month given expression in different ways to the corporate life of the British Medical Association. First in order was the Second Charles Hastings Memorial Festival at Worcester, made especially memorable by the sermon of the Dean and the Memorial Lecture by Sir Zachary Cope. An account of this event is published in this week's *Supplement*. The Winchester Division successfully followed the example of others in commemorating St. Luke's Day through the presence in Winchester Cathedral of all those many indispensable workers in the health field who make it possible for the doctor to see that his patients are cared for. And now, coinciding with the publication of this issue, is the Annual Clinical Meeting at Norwich in the heart of East Anglia.

METHODS OF LEARNING AND TECHNIQUES OF TEACHING

SECOND A.S.M.E. CONFERENCE

The second annual conference of the Association for the Study of Medical Education, on "Methods of Learning and Techniques of Teaching," was held at the Royal College of Physicians on October 15 and 16. The chair at the opening session was taken by Sir ROBERT PLATT, P.R.C.P., chairman of the association.

Incentives to Learning

Dr. W. D. WALL, director of the National Foundation for Educational Research, pointed out that much of the research so far on incentives and motivation had been on animals and children. It tended to ignore certain important factors in the case of adult humans, who functioned as part of a social situation rather than as isolated rats, and possessed a feed-back mechanism which as maturity increased made it more likely that they would repeat an action if they knew they had done well. Students came to the university with a record of success, and their first year or term might be decisive in deciding whether they would continue to be a success or modify their goals. Uncertainty on the part of the powers about the role the student should play helped to create anxiety, and he suggested that some thinking should be done about the role of the student in his first, second, and third years and after he had left medical school.

It would be worth examining whether students were being indoctrinated with authoritarian attitudes or attitudes of inquiry and suspended judgment, which were more difficult but more creative; whether students were being taught that medicine was competitive and highly individualistic, or co-operative; how far teaching and tutorial methods and the examination system implied competition and the praise-and-blame situation; how far particular methods of learning were imposed because teachers themselves had suffered under them; how far good groups of students could be drawn in to accept and profit from the democratic leadership of their teachers, so that the goals of group and teacher coincided; and how far allowance should be made for the anxieties of students by providing them with reassurance or outlets.

Sir ROBERT PLATT commented that this method of approach suggested that some kind of tutorial system was necessary in every medical school.

Student Rat and University Maze

Professor G. P. MEREDITH, professor of psychology at Leeds, said that in its own professional education medicine was finding that biological, clinical, and pathological information was not all that was required: the medical teacher had to understand the learning process in the student as well. The psychologist's theories on the subject were mostly derived from rats learning to run mazes, but students, unlike rats, were able to talk, and there was a striking difference between the university maze and the laboratory maze constructed by the psychologist himself, who knew it backwards. It was essential to see the maze through the eyes of the student.

He felt that an inquiry was needed into the "educational documentation" of the medical school and its exploitation by the student; this would involve a fact-finding probe into the students' habits of study and the documentary practices of medical teachers, a survey of existing systems and testing of experimental systems, the improvement of library facilities, and the creation of a working system of documentation. Work was proceeding on these lines in his department. Yet the university maze would not automatically be rendered more acceptable to the student rat by mechanizing and electrifying it, and research should take account of his profound biological need for orientation.

Less Anatomy

Dr. T. A. QUILLIAM outlined the steps already taken in the department of anatomy at University College, London, to disencumber the timetable and reduce the teaching of morphological detail. The time devoted to anatomy teaching had been reduced by about 100 hours over the last 10 years, and a dissecting manual of only 600 pages had been introduced.

Stiff oral examinations and leaderless discussion groups had been replaced by the "supervision" system, which enabled small groups of students to check whether a dissection task had been properly carried out with a tutor, who assessed the contribution made by each student to the work and discussion. Research seminars, in which a member of the staff described his current research work to the class, were a feature of the elective classes, which included also exercises in the collection of data from living people and clinical demonstrations by surgeons.

Teaching the Medical Sciences

At the afternoon session, the chair was taken by Dr. CHARLES NEWMAN.

Professor E. G. BALL, of Harvard University, said the basic problems in medical education on both sides of the Atlantic were not vastly different. In an effort to improve the training programme at Harvard, a special full-year course had been evolved which was designed to inculcate in first-year graduate students the ability to evaluate data and present results in a clear and concise manner. No rigid laboratory schedule was adhered to, the programme being moulded to the particular task in hand, and a special laboratory with a library attached had been constructed for experimental work. Students had a key to the building and were free to enter at any hour of the day or night. Staffing was by department members serving in rotation, so that new ideas were continually introduced. The course had stimulated the launching of research projects among staff members and had led to changes in the basic science curriculum for medical students.

Under a "guidance service," groups of six students were assigned a tutor who acted as their adviser and counsellor and with whom they discussed topics and problems. The system had helped to relieve their anxiety, and there had been a marked increase in the number of students wishing to spend the summer vacation working with a staff member on a research problem.

Value of Original Work

Dr. P. J. RANDLE, lecturer in biochemistry at Cambridge, said that originality ought to be encouraged in medical students provided a sense of responsibility accompanied it: they should not be taught to be original, but they should be given opportunities of showing originality. 99.9% of research activities followed a certain pattern; it was the thousandth experiment in which the unexpected might occur and important discoveries emerge, provided the research worker had the necessary perception. The attitudes and processes of clinical medicine, he suggested, were very similar to those of research, and, because research also offered opportunities for originality otherwise lacking in medical education, research could with advantage take its place in the training of doctors. At Cambridge additions and alterations were made each year to the lectures in the elementary course in biochemistry to keep up with advances in knowledge, and these captured the interest of undergraduates and made teaching more interesting for the teacher. Modern techniques widely used in research, such as photometry and chromatography, had become identified in the minds of undergraduates with progress through being made available in practical courses. In the Part II course opportunities were provided for tackling small research problems, and these had resulted in improved technical performance.

Turning to postgraduate research, Dr. Randle described the system at Cambridge leading to the Ph.D degree, in which research was performed under a supervisor and the student's other activities were strictly curtailed. It would

seem desirable, he said, that some of the principles which had proved valuable in this system should be applied to the M.D. degree.

Principles of Learning

Professor G. A. G. MITCHELL took the chair at the morning session on October 16.

Professor A. KENNEDY, professor of psychiatry at Edinburgh, said that studies were being conducted in his department to discover whether the curriculum could be altered so as to make students better doctors with the same amount of effort and without developing mental indigestion, and whether something could be learned from a general study of the learning process, or from specific medical studies, towards a fuller appreciation of principles as opposed to facts. One result from observations made at the medical schools in Durham and Edinburgh had been that students at Edinburgh were now given some information about methods of study at the beginning of the first year. The help received from students in effecting changes in teaching methods had been impressive, and the reports of the British Medical Students' Association on the preclinical curriculum had been excellent.

The transfer from school to university education was extremely important. Some students never achieved a university outlook, and the medical schools were often the graveyard of school reputations. The type of mind which stored facts as facts seemed to be inimical to the extraction of meaning and the formation of a framework of principles. Some memorizing was, however, essential, and this should be done when the student was fresh, always at very high pressure, and in large chunks rather than little bits, points being discussed during the process and revision carried out later. Memory-training systems had no value, and students should be discouraged from sending for books on the subject.

Learning from Patients

Professor M. L. ROSENHEIM, professor of medicine at University College Hospital, London, said that some countries laid special emphasis on the factual, which allowed an orderly sequence in teaching the scientific background of medicine at the expense of personal experience. But most students were motivated by the desire to help sick people and were eager for contact with patients. He was a staunch believer in the English system of the "firm," which combined factual teaching with student care of patients. He suggested that more use might be made of the medical emergency and that clerks should live in for part of their appointment. Out-patient clinics offered opportunities for students to observe how a doctor handled patients, and the follow-up clinic was often a suitable place for the senior student to study the long-term progress of disease and the effects of treatment.

Other points to which he drew attention were the importance of a critical atmosphere in the wards, the need for personal contact between the student and his tutors, and the desirability of discussing students' notes and recording their progress. He supported the view expressed by Dr. H. L. WILSON in the discussion which followed, that introductory courses were valuable and should not be abolished.

Visual and Auditory Aids

Professor J. K. RUSSELL, professor of midwifery and gynaecology at Durham, pointed out that much time and effort were needed to produce good teaching aids. Perhaps the time had now come to take a professional interest in this matter. In his own hospital, he had arranged for a room to be set aside where ward teaching could be amplified by means of teaching aids, the equipment including a projection screen for colour transparencies, a cabinet for the transparencies, and a viewing glass. Students could be taken straight from the ward and shown other examples of the same condition by means of slides, and could compare one condition with another. He had also begun to experiment with sound recordings because gynaecological patients were often reluctant to discuss their history in front of students. Tape recordings, however, could be played back to the students afterwards.

The chair at the afternoon session was taken by Sir RUSSELL BRAIN.

In a general talk on visual aids, Dr. R. C. MAC KEITH (Guy's Hospital) said there had been a great swing towards the use of visual stimuli in formal education, and he did not share the view that a good teacher did not need visual aids. They could contribute to four broad aims of medical teaching—experience, understanding, skill, and attitude. Photography and illustration had already gained acceptance. The usefulness of the film ought to be considered.

Those preparing slides for teaching purposes often overlooked the fact, which he demonstrated to the conference, that clear lettering was required to make them legible to people at the back of the room. It was worth taking trouble over visual aids, and they should always be comprehensible to a person seeing them for the first time.

Tutorial System at Oxford

Dr. JOHN BADENOCH, the director of clinical studies, described the Oxford tutorial. It offered opportunities for free discussion between tutor and student, for adapting the course of study to the requirements of the individual as well as helping him to discover and develop his own resources, and had long been the mainspring of the Oxford undergraduate. Tutorials were introduced into the clinical course in 1948, and they had since revised the scheme.

The new scheme required fewer tutors than before, and could be introduced on a modified scale even with a considerably larger number of students than at Oxford. The student would remain with the same tutor for the whole three years of his clinical course and would meet him monthly. The tutors would each devote one hour a week to the work and as far as possible would be drawn from senior men from the university departments and consultants with wide clinical experience. A larger group of more junior teachers would be responsible for talking to students in small groups and ensuring that each field in medicine and surgery was covered in the time available; these discussions would take the form of seminars related to the work students were doing in the wards and clinics. Ward seminars were a well-tried form of hammering home lessons learned at the bedside, provided the student was made to do the work.

Evaluation of Teaching Techniques

The final address was given by Professor M. WEATHERALL, professor of pharmacology at the London Hospital. It was important, he said, to make a distinction between "I think" and "I know: I have the evidence," and objective evaluation of methods of teaching was necessary. Controlled experiments could be made by dividing in some way either the material to be taught or the students being taught, and making comparisons between two groups. Operational research could also be carried out on the basis of records alone, as by comparing the outputs of different medical schools in order to arrive at conclusions about the teaching in these schools.

Professor Weatherall discussed various ways of evaluating the effects of teaching. Professional examinations were too unstandardized to be used as a technique. Professional career and conduct were an evaluation that mattered, but a survey such as that carried out in North Carolina was difficult, time-consuming, and expensive. Student opinion, on the other hand, could be equated, with a view to adopting the teaching methods best suited to the students. The conventional essay-type examination produced many points of view but was not perfect as a measuring instrument. For accurate evaluation, short-answer tests or multiple-choice tests with a number of alternative answers were preferred. One such test had shown that lectures were more effective than reading in enabling students to learn, and that some lecturers got decidedly better results than others.

STAGING OF BREAST CANCER

TRIAL OF T.N.M. METHOD

The International Union Against Cancer, through its committee on clinical stage classification and applied statistics, is recommending a 5-year clinical trial of the T.N.M. method* of staging breast cancer. The trial will be international in scope and start in January, 1960. The International Union has produced a booklet, entitled "Malignant Tumours of the Breast: Clinical Stage Classification and Presentation of Results," describing the method and the trial. Copies of the booklet may be obtained from Professor P. F. Denoix, Institut Gustave Roussy, Villejuif, Seine, France.

T.N.M. Classification

The following is the classification adopted in the T.N.M. system:

T = PRIMARY TUMOUR

T1.—Tumour of 2 cm. or less in its greatest dimension; skin not involved, except in the case of Paget's disease confined to the nipple; no retraction of nipple; no pectoral-muscle fixation; and no chest-wall fixation.

T2.—Tumour more than 2 cm. but not more than 5 cm. in its greatest dimension, *or* incomplete skin fixation (tethered or dimpled), *or* nipple retraction (in sub-areolar tumours), *or* Paget's disease extending beyond the nipple; no pectoral-muscle fixation; and no chest-wall fixation.

T3.—Tumour more than 5 cm. but not more than 10 cm. in its greatest dimensions, *or* skin-fixation complete (infiltrated or ulcerated), *or* peau d'orange present in the tumour area, *or* pectoral-muscle fixation (incomplete or complete); and no chest-wall fixation. (*Note:* Incomplete pectoral-muscle fixation indicates that contraction of the pectoral muscle limits the mobility of the tumour. Complete pectoral-muscle fixation indicates that contraction of the pectoral muscle abolishes the mobility of the tumour.)

T4.—Tumour of more than 10 cm. in its greatest dimension, *or* skin involvement or peau d'orange wide of the tumour but not beyond the breast area, *or* chest wall fixation. (*Note:* The chest wall includes the ribs, intercostal muscles, and serratus anterior muscle; it does not include the pectoral muscle.)

N = REGIONAL LYMPH NODES

N0.—No palpable homolateral axillary lymph nodes.

N1.—Homolateral axillary lymph nodes palpable but movable.

N2.—Homolateral axillary lymph nodes fixed to one another or to other structures.

N3.—Homolateral supraclavicular or infraclavicular lymph nodes movable or fixed, *or* oedema of the arm. (*Note:* Oedema of the arm may be caused by lymphatic obstruction; in such circumstances lymph nodes may not be palpable.)

M = DISTANT METASTASES

M0.—No evidence of distant metastases.

M.—Distant metastases, including skin involvement wide of the breast, involvement of the contra-lateral lymph nodes or breast, and all cases with clinical or radiographic evidence of metastasis to lungs, pleural cavity, skeleton, liver, etc.

Clinical Stages

STAGE I.—Tumour of 5 cm. or less (T1 or T2); skin fixation absent (T1) or incomplete (T2); nipple may be retracted (T2) or Paget's disease may be present (T1 or T2); pectoral-muscle fixation absent (T1 or T2); chest-wall fixation absent; no homolateral axillary nodes palpable (N0); no distant metastases (M0).

STAGE II.—Tumour of 5 cm. or less (T1 or T2); skin fixation absent (T1) or incomplete (T2); nipple may be retracted (T2) or Paget's disease may be present (T1 or T2); pectoral-muscle fixation absent (T1 or T2); chest-wall fixation absent; homolateral axillary nodes palpable but movable (N1); no distant metastases (M0).

STAGE III.—Tumour of more than 5 cm. in diameter (T3 or T4), *or* skin fixation complete (T3) or skin involvement wide of tumour (T4), *or* peau d'orange present in tumour area (T3) or wide of tumour (T4), *or* pectoral-muscle fixation incomplete or complete (T3), *or* chest-wall fixation present (T4), *or* homolateral axillary nodes fixed (N2), *or* oedema of the arm (N3), *or* homolateral supra-clavicular or infra-clavicular nodes movable or fixed (N3); and no distant metastasis (M0).

STAGE IV.—Distant metastasis present (M) regardless of the condition of the primary tumour and regional lymph nodes.

Stage Grouping

These four stage-groupings are therefore designated by the T.N.M. symbols as follows:

STAGE I.	T1 N0 M0 T2 N0 M0
STAGE II.	T1 N1 M0 T2 N1 M0
STAGE III.	T1 N2 or N3 M0 T2 N2 or N3 M0 T3 N0, N1, N2, or N3 M0 T4 N0, N1, N2, or N3 M0

STAGE IV.—Any combination of T and N symbols including M.

Special Studies

Among the particular points to which the International Union Against Cancer suggests special attention should be given during the trial period are the following: (1) The subdivision of "pectoral-muscle fixation" (in T3) into two: T3(a) incomplete, and T3(b) complete. (2) The subdivision of "homolateral axillary lymph nodes palpable but movable" (N1) into two: N1(a)—nodes not considered to contain growth, and N1(b)—nodes considered to contain growth. (3) The subdivision of "homolateral axillary lymph nodes palpable but movable" (N1) into two: N1(x)—node single, and N1(y)—nodes multiple. (4) The subdivision of "homolateral axillary lymph nodes fixed" (N2) into two: N2(a)—fixed to one another; N2(b)—fixed to adjacent structures.

*See Harmer, M., *Brit. med. J.*, 1958, **1**, 767

MEDICAL DEFENCE SOCIETIES

Each year the annual reports of the medical defence societies provide sober reading for practising doctors. It is customary to find in them reviews of recent court cases in which doctors have figured and accounts of hearings before Service Committees for alleged breaches of the terms of service. In addition statutory changes and other juridical matters affecting the practice of medicine are noted. A bare recital of the cases recorded shows how year after year the same mistakes are made, the same disasters occur. No doctor can afford to neglect these pointed reminders.

Medical Protection Society

The annual report of the Medical Protection Society, presented at the Society's annual meeting on October 7, contains, for instance, accounts of the following cases: amputation of a leg after inadvertent ligation of arteries at an operation for varicose veins; a missed fracture of the femoral neck; nerve damage after a thiopentone injection; gangrene resulting from the use of an unpadded plaster; forceps left in the abdomen; an operation performed on the wrong side; paralysis of a leg after spinal anaesthesia; pressure sores from a splint; a swab left behind at operation; and the discovery of a reamer in a bronchus after dental treatment. And these are not all.

The report also discusses the recovery of professional fees, Health Service and G.M.C. cases, medical evidence in the courts and at inquests, and witness fees.

The Medical Protection Society had a membership of 34,488 on December 31 last. During the year 2,114 new cases were referred to it. The annual expenditure was £80,000, of which £50,000 represented the cost of legal expenses in defence of members and indemnities against adverse costs and damages. The funds available for defence (including the Guarantee Fund) stood at £236,000. Further information may be obtained from the Secretary of the Society, Dr. ALISTAIR FRENCH, Victory House, Leicester Square, London, W.C.2.

Medical Defence Union

The M.D.U. broke new ground this year by holding its annual meeting in Dublin for the first time. The meeting

was on September 15 and the address was given by Dr. P. T. O'Farrell. The year also saw the retirement of Dr. Robert Forbes, who was Secretary of the Union for 25 years, from 1935 to 1959. A special appreciation of his work appears in the report.

Prominence is given in this year's report to cases arising from complaints by patients or their relatives to executive councils, of which 140 were dealt with during the year. The procedure is explained, with illustrative cases of both appearances before Service Committees and appeals against their findings. The Opticians Act is discussed, practitioners are reminded of their legal liabilities for third-party accidents on their premises, and advice is given on the handling of a Jehovah's Witness who refused a necessary blood transfusion. There are sections on disputed accounts, fees for the emergency treatment of road accidents, breach of copyright by a drug firm, inquests, the risks of ship surgeons, and the "duty to warn" about possible hazards of treatment.

The Medical Defence Union had a membership of 48,470 on July 21 last. During the year 2,688 cases were handled. Expenditure during the year was £111,000, of which some £67,000 represented legal charges, disbursements, and indemnity claims. The total funds of the Union (including the Guarantee Fund) were £143,662. Further information may be obtained from the Secretary of the Union, Dr. Philip Addison, Tavistock House South, Tavistock Square, London, W.C.1.

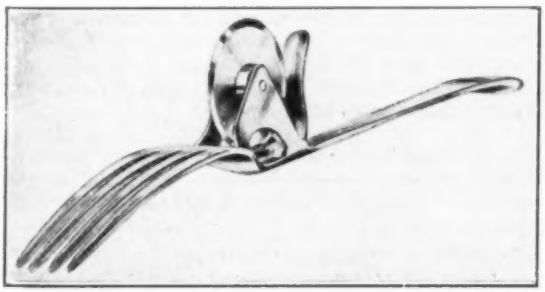
New Appliances

INSTRUMENT FOR ONE-ARMED PATIENT

Dr. H. B. Porteous, consultant geriatrician, Halifax Group of Hospitals, writes: The supply of gadgets for the handicapped is a challenge ever present with those dealing constantly with such people. Many have to be fitted to the individual patient, so that there is a tendency to multiply the numbers of those available. However, I make no apology for drawing attention to the one illustrated here and developed in the rehabilitation ward at St. John's Hospital, Halifax.

The usual implement available for the one-armed patient (and the hemiplegic able to use only one hand) is the combined knife and fork, which has not been as satisfactory as could be desired in a cutting instrument. The present utensil, developed by Mr. T. L. Parker, charge nurse of the rehabilitation ward, consists of a dinner-fork on the back of which a stainless-steel wheel with a keen edge rotates on a pivot in a guarded gallery.

It has been fitted so that the patient is able to cut up food without the difficulty experienced with the usual combined knife-fork. It has been tried in several wards other than the one in which it was developed, and also by out-patients at the occupational therapy department of the Halifax General Hospital, and very favourable comments were obtained from all users.



The prototype reproduced in the accompanying photograph was made by Messrs. P. V. O'Neill Limited, Surgical Appliance Specialists, 33, Kirkgate, Shipley, Yorkshire, who modified the ordinary hospital dinner-fork supplied by us. The cost of modifying this, I believe, is under £1. The hospital dinner-fork lends itself admirably to this modification, as it is a very sturdy instrument, rather more so than the average domestic fork.

MODIFIED GREEN-ARMYTAGE CAESAREAN SECTION CLAMP

Mr. John F. Foulkes and Professor J. C. McClure Brown, of the Institute of Obstetrics and Gynaecology, Hammersmith Hospital, London, write: The tearing of the posterior wall of the vagina while stripping down the rectum during a colpoperineorrhaphy is a common experience in gynaecological surgery. That this might be prevented by the use of a pair of forceps with a wide and firm grip seemed a probability to one of us (J. F. F.); an instrument fulfilling these requirements is Green-Armytage's caesarean section clamp.

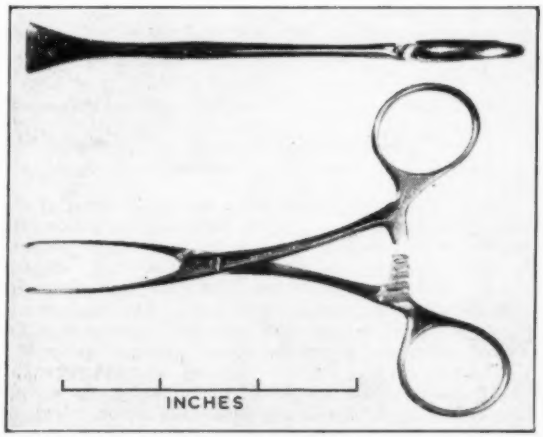


Fig. 1

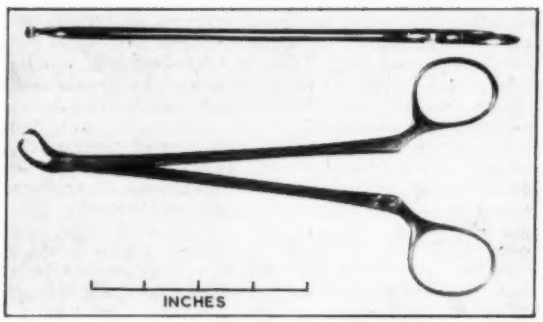


Fig. 2

The application of two of these clamps to hold the cut edge of the posterior vaginal wall after the initial transverse incision was found almost to eliminate tearing of the mucosa whilst the rectum was being separated from it.

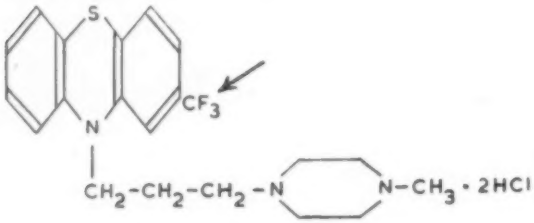
Because the long handles handicapped their application to this work, the modification of shortening them was suggested (J. C. McC. B.). The models made to these specifications (by Bailey & Co.) are shown in Fig. 1, and are now regularly used by us.

The angled Allis forceps (Fig. 2) (also made by Bailey) are designed (by J. C. McC. B.) to catch the utero-sacral ligaments during the operative repair of enterocoele.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Stelazine (Smith, Kline, and French).—The approved name of this drug is trifluoperazine, and its chemical name is 2-trifluoromethyl-10-[3′-(4″-methyl-1″ piperazinyl) propyl] phenothiazine. It is a derivative of prochlorperazine, from which it differs by having CF_3 instead of Cl in the position marked by an arrow on the structural formula below.



Clinical Effects.—Trifluoperazine is the most active of the phenothiazines and more potent than chlorpromazine; its effects are long lasting, and it is reported to be safe for long-term therapy. Its onset of action is rapid; clinical effects, including control of disturbed behaviour in psychiatric patients, occur within five or six days. Intramuscular medication is often necessary initially in daily divided doses of 1–3 mg. for acutely disturbed patients—e.g., acute mania, delirium tremens, or schizophrenia. Intramuscular medication should not exceed 5 mg. a day, and, because of the drug's long duration of action, injections should not be given more often than four-hourly. Once the acute disturbance is brought under control, oral medication is substituted.

Trifluoperazine has also been used successfully in the treatment of patients with mild mental and emotional disturbances, including anxiety and tension states, and for relief of gastro-intestinal manifestations of emotional tension, anxiety, headaches, and tension syndromes associated with menstruation or childbirth.

Side-effects.—These usually appear and are usually restricted to the first two or three weeks of therapy. At the higher dosage range extrapyramidal symptoms often appear, consisting of Parkinsonism or dystonic manifestations. They can be reversed by lowering the dosage or by giving anti-Parkinsonian drugs. Motor restlessness, insomnia, and a feeling of jitteriness sometimes occur. Other infrequent side-effects are dizziness, dryness of the mouth, and blurring of vision. Jaundice, contact dermatitis, and blood dyscrasia have not been reported, but are worth bearing in mind as possible complications.

Contraindications.—The drug is contraindicated for comatose and stuporous patients, and must be given with caution when cardiovascular function is seriously impaired or when administered with barbiturates, opiates, or other sedatives and narcotics.

N.H.S. basic price: Tabs. 1 mg., 50 for 9s.; tabs. 5 mg., 50 for 11s. 4d.; amps., 1 mg. in 1 ml., 1s. 6d. each.

The ideas of WILLIAM TUKE, who founded the Retreat at York in 1792, played a large part in the planning of the new $2,520,000 Padre Billini Mental Hospital in the Dominican Republic. This tribute was paid by the Republic's Health Minister, Dr. JOSE SOBA, when he opened the hospital, which covers 42,000 square metres, and consists of 36 inter-communicating buildings for patients and staff. It is the largest of the new hospitals completed under the Trujillo medical plan.

Correspondence

Heredity in Breast Cancer

SIR,—In your leading article "Heredity in Breast Cancer" (*Journal*, October 10, p. 683) you state: "It is evident, in the first place, that a virus, such as the milk factor detected by J. J. Bittner in mice, cannot be very significant in man. If it were prevalent, a strong predominance of affected maternal aunts and grandmothers, as opposed to paternal aunts and grandmothers, would have been expected."

Without wishing to press the view that the "Bittner factor" might play any part in the production of human breast cancer, it is necessary to point out that the above argument does not exclude it. It can be shown in the mouse that the factor can be transmitted from the male to the female—for instance, in the semen. The infected female then transmits the factor in the milk to her offspring. This being so, no considerable predominance of maternal relatives, as opposed to paternal relatives, need be expected amongst the affected propositi.—I am, etc.,

London, N.W.1. HEDLEY ATKINS.

SIR,—I was very interested to read your leading article (*Journal*, October 10, p. 683) on heredity in breast cancer. A study of the relation between diseases and physique has been made at the Presbyterian Hospital in New York.[1] Physique was measured and classified according to Sheldon's technique.[2] It was found that, in a consecutive series of 100 cases of carcinoma of the breast in women, there was an impressive grouping around somatotype 451. As the somatotype is a measure of the hereditary constitution of the individual, albeit an imperfect one, this provides further strong evidence of the hereditary nature of carcinoma of the breast in women.

The determination of the somatotype would be a useful way of estimating whether or not a woman had such an inherited disposition.—I am, etc.,

Southport, Lancs. J. H. MOTT.

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1 Sheldon, W. H., Hartl, E. M., and McDermott, E., *Varieties of Delinquent Youth*, 1949. New York.
2 —— Stevens, S. S., and Tucker, W. B., *The Varieties of Human Physique*, 1940. New York.

Birth Weight and Maternal Smoking

SIR,—Dr. C. R. Lowe is to be congratulated on his clear demonstration that a certain type of woman tends to possess in common the attributes that she smokes during pregnancy and that her foetus is underweight (*Journal*, October 10, p. 673). However, one wonders how long it will be before the accumulators of such data realize that, because among the population of the British Isles there is an association between addiction to haggis and a liking for the music of the bagpipes, indulgence in the former delicacy does not necessarily cause a predilection for cacophony.

It is a pity that the presentation of these data is marred from beginning—"Effect of mothers' smoking habits on birth weight"—to end—"smoking during pregnancy substantially retards foetal growth"—by such dubious logic.—I am, etc.,

D. F. HAWKINS.

Department of Obstetrics and Gynaecology,
Hammersmith Hospital,
London, W.12.

Reduction of Benzpyrene in Tobacco Smoke

Sir,—In 1956 Alvord and Cardon[1] showed that a number of compounds, notably ammonium sulphamate, were effective in reducing the amounts of 3:4-benzpyrene in the combustion products of tobacco and paper, and they claimed that, by using cigarette paper containing 4.25% of ammonium sulphamate, the mainstream smoke of the cigarettes contained less than half the amount of 3:4-benzpyrene than the smoke from untreated cigarettes.

According to experiments carried out in the tobacco industries' laboratories, two compounds, copper nitrate and platinum diamino-nitrite, reduce the benzpyrene content of cigarette smoke, but the effect claimed by Alvord and Cardon could not be substantiated.[2] We have repeated the work of these latter investigators and have confirmed that the amounts of anthracene, 3:4-benzpyrene, fluoranthene, and pyrene in the mainstream smoke are all greatly reduced by treatment of the paper with ammonium sulphamate. A full account of this work will be published as soon as possible. We have also found by the co-operation of about 40 smokers that it is impossible to detect a difference between the treated and untreated cigarettes by smoking them.

Although the carcinogenic substances reported present in tobacco smoke now number 14 different compounds, the most potent of them is still 3:4 benzpyrene, which is reported to varying extents from 1 to 10 micrograms in the smoke from 100 cigarettes. Such small amounts are said to be unlikely to be a causal factor in lung cancer,[3] but even quantities as small as this in the presence of promoters[4] have been shown to produce skin tumours in experimental animals. It is possible that similar promoter action may occur in lung tissue. In any case reduction of the small proportions of benzpyrene to even lower amounts is an object worth attaining, and the pre-treatment described is one way of doing this.

Other methods of reducing the risks attendant upon smoking cigarettes without smoking fewer are by smoking to longer stubs,[5 6] and also by using porous or perforated paper[7 8] so as to cool and dilute the later smoke and thus reduce the total smoke condensate.[9] Employment of all these methods should reduce risks due to taking in smoke compounds to a fraction of what they otherwise would be.

We acknowledge with thanks the gift of cigarettes from the Rand Development Corporation of Cleveland, Ohio, U.S.A.

—We are, etc.,

Sir John Cass College, London, E.C.3.
Arthur J. Lindsey.
Kimraj Persaud.
Adele Candeli.
Istituto d'Igiene dell'Università di Perugia, Italy.

References

1 Alvord, E. T., and Cardon, S. Z., *Brit. J. Cancer*, 1956, **10**, 498.
2 Tobacco Manufacturers' Standing Committee (6–10, Bruton Street, London, W.1). Report for Year Ending May 31, 1958.
3 *Rep. med. Res. Coun. (Lond.)*, for 1955-6, 1957, Cmnd. 180, p. 12. H.M.S.O.
4 Roe, F. J. C., personal communication.
5 Doll, R., Hill, A. B., Gray, P. G., and Parr, E. A., *Brit. med. J.*, 1959, **1**, 322.
6 Hammond, E. C., ibid., 1958, **2**, 649.
7 Lindsey, A. J., ibid., 1959, **1**, 506.
8 Smyth, C. N., ibid., 1959, **1**, 506.
9 Lindsey, A. J., *Brit. J. Cancer*, 1959, **13**, 195.

Needle Biopsy of the Pleura

Sir,—I was interested to see in your issue of September 19 (p. 478) Dr. P. O. Leggat's report of needle biopsy of the pleura in 20 cases of malignant pleural effusion. In this area we have used the method routinely for over two years, and I can fully confirm its value in the field of tuberculous and malignant pleural effusions. Perhaps you would allow me to add some comments to Dr. Leggat's remarks.

We have used throughout the so-called Abrams or Harefield needle, which, like Dr. Leggat, we find superior to the Vim-Silverman needle generally favoured in America. Our series of malignant effusions now comprises 29 cases. Of these, 17, or 59%, were diagnostic, and in one case the specimen was inadequate. These results largely agree with other published reports, but a further breakdown of the group brings out some interesting points.

The most frequent condition, as expected, was bronchial carcinoma, of which there were 19 cases. Nine of the 19 biopsies were positive, a rate of 47%, which seems at first sight disappointing. It must be pointed out, however, that practically all these cases were examples of the peripheral type of carcinoma, in which the diagnosis is notoriously difficult. 17 of the 19 cases were negative on bronchoscopy, while cytology of sputum and pleural fluid yielded only two positive results.

The other interesting group in this series was that of pleural effusion in women with a previous history of carcinoma of the breast. One cannot automatically assume that all such effusions are metastatic, and a definite diagnosis is essential, particularly in view of the more hopeful methods of treatment now available. Such cases are not rare, and in 18 months we had seven patients, six of them following mastectomy and radiotherapy. Pleural biopsy was positive in six, while in the seventh case the nature of the effusion is still *sub judice*.

One patient was of special interest. This was a woman of 64, who complained of cough and pleuritic pain of eight days' duration. A large, slightly blood-stained effusion was found and a Mantoux reaction 1 in 10,000 was positive. Routine pleural biopsy showed well-differentiated adenocarcinoma. On further clinical examination skin-thickening and slight retraction of the nipple was found in the right breast, with palpable right axillary lymph nodes. Carcinoma of the breast first presenting with a metastatic pleural effusion was therefore diagnosed.

I would like to add that no significant complications were noted in over 90 biopsies so far done, and we find the method entirely suitable for routine use in all cases of pleural effusion where aspiration of the chest is indicated.—I am, etc.,

Reading, Berks. A. J. Karlish.

German Medicine Abroad

Sir,—Professor W. C. W. Nixon's observations in the *Journal* of October 10 (p. 693) on the decline of Britain's influence overseas come as no surprise to those who have knowledge of conditions abroad during the last few years. In times past, Britain's reputation was the envy of the world; and in the underdeveloped countries she was the hope, the aspiration, and often the Mecca of their peoples. To-day, by default, her place is being taken by other nations—not only by Germany, as Professor Nixon so clearly describes, but also by Russia and the United States. The underdeveloped countries are being "sold" the Russian and American way of life, and money, men, and materials are lavishly being poured into these countries.

I, personally, feel most strongly that we have a duty to tell the underdeveloped countries something about the British way of living—the way of compromise and fair play, the way of evolution in an imperfect world. Probably the best way to achieve this to-day is to send undergraduates, teachers, engineers, doctors, and those of other vocations overseas on secondment, and also to make it easy for Commonwealth and foreign nationals to train here in Britain.

It must not be forgotten that the underdeveloped countries have few educated people in their populaces and that their students who are being educated to-day will be the rulers of to-morrow. If these students are trained in Britain or by or with British expatriates in their own countries, they have a vested interest in Britain and all that she stands for. In support of this I would refer to Professor Alexander Brown, of Ibadan, who last year at the British Medical Association Conference on Recruitment Oversea observed that we can influence the pattern of development at the new colonial universities for many, many years if we act *now*, by making recruitment from this country easy.

But there is another reason, as Professor Nixon mentions, and that is the loss of ground in the economic field; we must "export or bust." I believe it true to-day that trade depends on confidence, and no little part of this is confidence in the people who produce the goods for sale; it is for this reason that the "import and export" of professional personnel has a tremendous impact on trade. It used to be said that trade followed the missionary, but to-day it can be said that trade follows the teacher.

Many organizations in this country are attempting to tackle the problems I have outlined, but some are without adequate funds, some are hampered by red-tape, and others are, frankly, ineffective. The time has come when the Government must take the lead by encouraging Britishers to go overseas as part of their training for a career, and more foreign nationals to study in this country.

To make this possible there are two needs to be fulfilled. The first is to persuade (or direct?) the universities, the education authorities, the National Health Service, and the private corporations, and industry, that service overseas would in the long run be advantageous, both to themselves and to the careers of their employees (in fact, it could be an accepted part of training). The second is to provide the finances to implement this policy. My answer to the Jeremiahs on this point is that we *must* find the money—if we cannot afford to be in the van of interplanetary progress, we can at least lead in social progress on this planet. Only by a deliberate policy at high level can Britain, now living on the economic fat put on by former generations, continue to maintain her weight in the world, and by so doing help in its development, and, incidentally, help to keep her own economic stability.—I am, etc.,

Department of Pathology,
Royal Free Hospital,
London, W.C.1.

KENNETH HILL.

SIR,—I should like to support wholeheartedly Professor W. C. W. Nixon's findings (*Journal*, October 10, p. 693). My experience during visits to Athens, Istanbul, and Yugoslavia was similar to his, though, in addition to his comments on the availability of medical textbooks being predominantly American and German, I would also add French. I would also mention that anatomy textbooks in French, for instance, were in common use, partly perhaps due to the fact that in certain districts of Greece, at any rate, French is more readily understood and spoken than is English, and postgraduate experience in Paris is considered to have immense prestige value.

Great as is our responsibility towards the countries of the British Commonwealth, Great Britain is, after all, geographically, at any rate, part of Europe, and at times one wonders whether this fact is completely overlooked. —I am, etc.,

London, W.1. G. M. SANDES.

Service Psychiatrists

SIR,—Psychiatrists should indeed be grateful to Mr. Michael Harmer (*Journal*, October 10, p. 696) for his timely lesson in humility. To have specialized in one branch of medicine, and yet have acquired so profound a knowledge and such unerring judgment in other specialist fields, is an achievement that must surely inspire in the mere psychiatrist a condign sense of admiration and awe. One cannot but be impressed by the criticism, in 800 words, of a review of "over 1,200 words" which, it would seem, so disproportionately occupied your "precious space."

As the author of the work on Army psychiatry, the review of which Mr. Harmer feels so competent to judge, it would be presumptuous indeed to expect that one so versed in the several branches of medical science would even glance at a book such as mine: in view of the overwhelming evidence of his remarkable psychiatric experience and case histories, this would obviously have been superfluous.

It is, nevertheless, a fact that I mentioned the views of General Patton, Lord Cherwell, and others (medical and non-medical), who were convinced that psychiatry was worthless and harmful, and that we were charlatans. The minute addressed by Mr. Churchill to the Lord President (which is quoted by Mr. Harmer, and occupies not a little of your valuable space) was quoted by me, and later, in the debate on the Mental Health Bill (*Hansard*, Commons, January 26, 1959, **598**, 729–30), by Dr. Summerskill, who, I think, stated quite fairly in this connexion that the then Prime Minister "can be exonerated because . . . among his manifold activities he has never studied psychological medicine. He was the recipient of prejudiced and ill-informed advice." Also, although not necessarily conducive to humility, it may be recalled that there was a time, in medical history, when even surgeons were among the "camp-followers" (and the R.A.M.C. as such dates only from 1898).

From the importance attached by Mr. Harmer to the medical opinions of such eminent laymen, are we to assume that surgeons in the Services habitually availed themselves of the "professional" advice of these gentlemen? The fact that General Wingate, for example, did not believe in the value of tropical medicine and hygiene, and would not accept expert medical advice in this respect, did not deter our non-psychiatric colleagues in Assam and Burma from carrying out, so far as possible, their duties according to their professional experience and conscience. It is well to remember, in any case, that Army psychiatrists also received support, in personnel and officer selection, and in other matters, for example, from Generals Wavell, Auchinleck, Eisenhower, and others (medical and non-medical).

I feel confident that Mr. Harmer's generous statement, that Service psychiatrists "probably did as much good as the undoubted harm they also did," will help

psychiatry to "rid itself of its inferiority complex." Doubtless there are good psychiatrists and bad ones: is it conceivable that this might also be true of surgeons?

Finally, I would refer to a quotation (of 1785) at the beginning of my book, which may not be entirely irrelevant here:

"But nothing affords a more humiliating view of human wisdom, than when we see men of real learning and skill in particular branches, treating the scientific pursuits of others with contempt. How much soever such men may excel in their own science, and how lofty and important soever that science may be, they can neither be esteemed true philosophers, nor friends of mankind."

—I am, etc.,

Bransgore, Hampshire. R. H. Ahrenfeldt.

Sir,—May I say how much I agree with most of the views expressed by Mr. Michael Harmer (*Journal*, October 10, p. 696)?

In the winter of 1942–3 I was commanding the field ambulance attached to an infantry brigade holding the Medjez-el-Bab salient in Tunisia. One morning, two Army psychiatrists arrived at my headquarters and asked to be shown a battalion position. Neither I nor any of my officers had yet met this new kind of R.A.M.C. specialist, described by Professor Crew (*Journal*, September 26, p. 551) as "young men who were quite outstanding in respect of their intellectual equipment." That afternoon I took the two youngsters (both of them my senior by some years) to see two regimental aid posts. One was sited in the ticket office of Medjez Station, which was shelled during our visit. The other was in a dug-out some 2,000 yards from the notorious Longstop Hill, then occupied in some strength by the Germans. By a coincidence the battalion C.O. was also visiting his R.A.P. when we arrived, and he took the opportunity of giving my guests his views on the morale of the infantry soldier as affected by the presence in N. Africa of R.A.M.C. psychiatrists. I was sorry for my companions, who, ever since the shelling of the station, had been exhibiting symptoms of what I now know to be an acute anxiety state. When we got home, they politely refused my offer of a bed for the night, and departed whence they came. Unfortunately for me, the news of their adventure reached the ears of my brigadier, a very fierce man indeed, and I was given in no uncertain terms his orders as to the disposal of any future "trick-cyclists" who might visit his brigade area. None did.

Only once in 2½ years had I to place one of my own men on a court-martial charge of cowardice in the face of the enemy. A member of a squad of stretcher-bearers going up to relieve some of his friends in an unpleasant part of the line, he ran rapidly in the general direction of Algiers, and was not found for two days. The psychiatric report on this man had the effect of reducing the charge to one of absence without leave, and after serving a short sentence he was posted for duty to a base hospital. Thereafter I was never quite certain that his action might not be repeated by some tired and badly frightened man who, needing the moral support of his own self-respect and an inflexible discipline, had had his attention drawn to an easy way out.

In the summer of 1940, soon after the Dunkirk evacuation, I was ordered one day to report to the Royal College of Physicians, where I was invited, together with four or five other junior medical officers, to give my impressions on the morale of the troops at Dunkirk to the P.R.C.P., then Sir Charles Wilson. As far as I know there were no psychiatrists at Dunkirk, otherwise perhaps their ideas would have been obtained rather than ours, ideas which we liked to think were perhaps passed on to the Prime Minister at one of those legendary war-time breakfasts. I have often thought that, if my views on morale had been sought three or four years later, I should never have been able to support the activities of my psychiatric colleagues, whose opinions on certain court-martial candidates had, so frequently, such a devastating effect on the morale of the fighting troops.

No, Sir, Mr. Michael Harmer is too generous when he says, "On balance they probably did as much good as the undoubted harm they also did."—I am, etc.,

Reading. Richard G. M. Keeling.

Sir,—Mr. Michael Harmer's contribution on the above subject (*Journal*, October 10, p. 696) is of considerable interest. While the examples he quotes were not, I hope, typical of Service psychiatry, I think it must be admitted that the teaching and practice of psychiatry requires an "agonizing reappraisal."

In my experience, many of the younger psychiatrists have a facility for theorizing and philosophizing, but are singularly lacking in the groundwork of their specialty. Kraepelin, to them, means only a name. Of McDougall's contribution to pure psychology they have almost no knowledge. They are usually equally ignorant of the groundwork of child psychiatry laid down by such writers as Adler and Cameron. Worse still, many of them have never taken the trouble to master the techniques of the physical methods of treatment, and thus avoid them so far as possible. It is not surprising, therefore, that when put to the test of practical efficiency many of them become "unstuck."

The solution of this problem is not immediately apparent. Unfortunately, as most psychiatrists are full-time officers, shoddy work carries no penalties. But psychiatry, with its amazing advances over the past 30 years, should have no "inferiority complex," which unquestionably it has. If the young psychiatrist will take the trouble (and perhaps be gently persuaded by examiners) to master his psychology, psychopathology, and modern techniques of physical treatment, and will then have the humility to be guided for some years in his practice by men of more mature experience, he will eventually acquire a proficiency of which he need not be ashamed. Psychiatric problems can now be solved with a precision and a success which, I think, compares very favourably with general medicine and surgery, but realistic thinking, based upon knowledge and experience, is essential, and all woolly theorizing and speculation should be ruthlessly cut out.—I am, etc.,

Pinner, Middlesex. Robert Thompson.

Complications of Prostatectomy

Sir,—Mr. J. Cosbie Ross and Mr. L. F. Tinckler mention in their valuable paper on prostatectomy (*Journal*, October 10, p. 663) that they employ an eyeless needle in closing the prostatic capsule; with this I would strongly concur. The Harris "boomerang" needle is a difficult instrument to employ efficiently with relatively untrained and constantly changing assistants, the needle is large and traumatic, and the hypothesis that one is more liable to prick the back of the pubis with an ordinary needle and to precipitate osteitis pubis appears without foundation.

A trainee surgeon struggling with a "boomerang" is strongly advised to abandon it in favour of a small round-bodied needle on a conventional holder; he will be delighted to find how relatively simple closure of the prostatic capsule then becomes.—I am, etc.,

The Radcliffe Infirmary, Oxford. H. Ellis.

Aetiology of Disseminated Sclerosis

Sir,—We refer to Dr. A. M. G. Campbell's letter (*Journal*, July 18, p. 72) in which he alludes to the prevalence of disseminated sclerosis in Queensland, Australia. We are at present attempting to estimate the prevalence of disseminated sclerosis and retrobulbar neuritis in Queensland and elsewhere, but unfortunately we are not yet in a position to report our findings. As a result of this study we hope to indicate the incidence of the disease in the aboriginal population, in native-born Australians of European extraction, and in those born elsewhere.

Figures furnished by the Commonwealth Bureau of Census and Statistics, Brisbane, indicate that in the period 1937–56 there were 212 deaths from disseminated sclerosis—a mean mortality rate of 0.95 per 100,000 of the population. If the average duration of disseminated sclerosis is taken as being 20 years, the expected prevalence in Queensland is 19 per 100,000, or in a population of approximately 1,400,000 there will be some 163 cases for all age groups over 19 years.

During the past three years 35 patients with disseminated sclerosis have been seen at the Medical Professorial Unit of the Brisbane Hospital. Inquiry regarding their birthplace furnished the following information: Australia 26 patients (Queensland 20 patients); Britain 5; Poland 2; New Zealand 1; and Greece 1. These figures are at variance with the view expressed by Allison and Millar,[1] who, quoting Selby, state: "The disease is comparatively rare in Australia, so that when a patient is seen the inquiry is made whether he comes from England." Thus far we have not encountered disseminated sclerosis in an aboriginal.

In view of the report by Campbell *et al.*[2] it is of interest that lead-poisoning has been, in the past, particularly common in Queensland.[3,4] We are informed by one of our colleagues (Dr. B. T. Emmerson), who is studying certain aspects of chronic lead-poisoning, that he has not encountered a neurological syndrome suggestive of disseminated sclerosis in his patients. We have, however, not investigated our patients with disseminated sclerosis for evidence of lead exposure. Queensland extends from latitude 10° 41′ to latitude 28° and covers an area of 670,500 square miles, 359,000 of which are within the tropics. The population north of the tropic of Capricorn is approximately 302,000 persons. It will thus be of interest to compare the prevalence rate in this area with that in the more temperate south.—We are, etc.,

J. M. Sutherland.
M. J. Eadie.

University of Queensland,
Brisbane, Australia.

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Treatment of Senile Vaginitis

Sir,—Dr. R. Murdoch and Dr. W. P. Black (*Journal*, October 10, p. 678) are to be congratulated on their thorough investigation of senile vaginitis and on their successful results obtained with dienoestrol cream. On a number of occasions, when vaginal soreness has been extreme, I have preceded treatment with stilboestrol cream by a proprietary preparation containing oestrogen, benzocaine, and amethocaine with rapid relief. Some elderly patients prefer to use a finger with which to insert the cream into the vagina.—I am, etc.,

London, W.1. M. Moore White.

"Neural Therapy"

Sir,—I see that the subject of neural therapy has attracted the attention of one of our leading national daily newspapers, and that a considerable amount of space has been devoted to explaining the underlying theories of this therapy to the lay public. It has always been a matter of some surprise to me that so little is known about neural therapy amongst my colleagues in Great Britain, when this method of treating severe pain is widely practised on the Continent. Indeed, a very large number of papers have been published over the last 25 years, and it would certainly require an extremely lengthy article to deal adequately with all the publications on neural therapy.

To understand the principles of neural therapy, we must get away from the conventions of Virchow's teaching and try to appreciate the basic theories of Ricker's "Relationspathologie"[1] and Speransky's experiments,[2] without prejudice. Virchow's theory has been universally acknowledged, and it has had a paramount influence on medical science as well as contributing to the understanding of the pathology of disease. Nevertheless, as Newton's theory was replaced by Einstein's theory of relativity, Virchow's teaching is about to be replaced by Ricker's pathology of relativity, and Speransky's neurodystrophy teachings. Into all this, Selye's theory of stress and adaptation[3] fits perfectly. We have to alter our conception of disease, starting with our views on inflammation and continuing right through to dystrophy and tumour formation. According to Ricker, the releasing cause of a disease is an unphysiological stimulus which affects primarily the nervous system, as a consequence of which a circulatory derangement occurs in the terminal circulatory area. What happens in the periphery depends on neurally controlled relations between the neural system, blood vessels, tissue fluid, and tissue nutrition. The maintenance of normal tissue structure is subject to a legitimate relationship between the neural stimulated bloodstream and the tissue. Similarly, according to Speransky, the nervous system is the centre of all physiological and pathological events. Disease is the reaction of the body to stimuli influenced by the nervous system, the centre of which, for autonomous regulation and co-ordination, lies in the hypothalamus.

Although following different paths, Ricker and Speransky come to the same conclusion in so far as they state that pathological stimuli, both endogenous and exogenous, primarily irritate the nervous system in an unphysiological sense, leading to dysfunction and subsequent dystrophy, heralding early—at first reversible—structural changes. Whereas Virchow's cellular pathology can aptly be called static, presenting irreversible changes in the body as "the disease," the teaching of Ricker and Speransky can be called fluent, in that it points out the train of events which lead to the fully developed disease. It reveals how distinct reciprocity between centre and periphery—principally along afferent and efferent neural pathways but also by humoral routes—influences the pathic events provoked by the defence mechanism of the body.

The work of these two scientists was later clarified by P. Stoehr, jun.,[4] F. Feyrter,[5] J. Boeke,[6] and others who,

using a new staining method, demonstrated minute details of nerve structures: the previously unknown ubiquitous terminal reticulum and its synapses with the peripheral target cells. The work of F. Eichholtz,[7 8] A. Fleckenstein,[9] and others on the mode of action of local anaesthetics has thrown further light on the claims made by Ricker and Speransky. The knowledge of neural pathology and relativity gained by H. Kalbfleisch,[10] W. Nonnenbruch,[11] H. Siegmund,[12] F. Hoff,[13] and others has also confirmed these new theories.

Thus, scientific explanation has been provided for a therapy originally introduced by C. L. Schleich[14] in 1894 and later by G. Spiess,[15] who both advocated the application of local anaesthetics for the relief of pain. Whereas G. Spiess established their anti-inflammatory effect, twenty years later Ferdinand and Walter Huneke[16 17] systematically developed the application of local anaesthetics to a special therapy which they called "curative anaesthesia." This therapy, now called neural therapy, in its broadest sense comprises all the methods which influence the dysfunction of tissue and tissue fluids by neural pathways. Further, it enables us to prevent and reverse dystrophies caused by stimuli, and, additionally, neural therapy brings quick relief and can promptly clarify a clinical picture.

Blocking regional ganglia should not normally be carried out by general practitioners, but the injection of local anaesthetics and the like into the respective body segments can suitably be carried out in any surgery, and the technique is not too difficult to learn. I have found in my six years' experience with neural therapy that it relieves pain and anxiety both efficiently and quickly. Furthermore, it has proved invaluable in making a diagnosis as a result of which, in many cases, it has not been necessary to send patients to hospital for further investigation. It is really remarkable that the English-speaking medical world has not yet acknowledged neural therapy, although years ago Mackenzie and Head, two Englishmen, laid some of the foundations.—I am, etc.,

London, W.1 ALBERT W. BAUER.

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Food Bolus Obstruction

SIR,—We read with great interest the article by Mr. D. G. L. Davies and Mr. R. H. Lewis on "Food Obstruction in the Small Intestine" (*Journal*, September 26, p. 545) and the article by Mr. M. F. Butler on "Orange-pith Ileus after Partial Gastrectomy" (p. 549), which brought to mind a similar case treated recently at the Caerphilly District Miners Hospital.

A woman aged 52 was admitted as an emergency with a history of vomiting and upper abdominal pain, colicky in nature, which had been present for 24 hours. The pain became increasingly severe and localized in the central abdomen. She had been constipated for the past two days, and had not passed flatus for one day. On examination her temperature was 97° F. (36.1° C.), pulse 90, dry tongue, distended abdomen with generalized guarding and tenderness. Rectal examination revealed no abnormality. A straight *x*-ray of the abdomen in the erect position revealed multiple fluid levels and a characteristic picture of small-bowel obstruction. At laparotomy the upper two-thirds of the small intestine was distended and a firm mass, 1½ in. (3.7 cm.) long, consisting of three segments of partly digested orange, was causing a complete obstruction. This was removed by enterotomy. The patient made an uneventful recovery. On questioning post-operatively, the patient stated that she had eaten an orange rather hurriedly the day before the onset of symptoms.

We thought it worth while to give a short account of our case to support the statement of the authors that the number of such reports is increasing, and to emphasize the importance of the conclusions drawn by the authors concerning the desirability of dietary advice. As in the history of our patient, we found neither partial gastrectomy nor defective teeth; the factor which brought about the obstruction was purely the inadequate and hurried mastication. This itself proves that the inadequate mastication of citrus fruits is a potential danger in causing intestinal obstruction, without regard to the patient's age. The prevention of the intestinal obstruction in general is a difficult problem, owing to the complexity of the causative factors. As the main aim of the modern conception of medicine is prevention, we think that this kind of obstruction can become a preventable disease, provided that the advice of the authors is carefully respected and made known.

We should like to thank Mr. Hugh Jenkins for permission to publish this case.

—We are, etc.,

ZOLTAN MERA.
PAUL KENNEDY HUNT.

Caerphilly and District Miners Hospital,
South Wales.

SIR,—The two papers by Mr. D. G. L. Davies and Mr. R. H. Lewis and by Mr. M. F. Butler (*Journal*, September 26, pp. 545 and 549) rightly emphasize the comparative frequency of this type of obstruction and the hazards of swallowing inadequately chewed pieces of orange, especially by those who have had a partial gastrectomy.

We have each operated on two cases of food obstruction of the lower ileum, the lowest site of obstruction being four inches (10 cm.) above the ileocaecal valve. The orange was responsible for three, while the fourth patient was laid low by an outsize meal of cod-roe and chips. Mr. Butler found only one case reported following the Billroth I gastrectomy, but in two of our three patients who had had a gastrectomy the operation was of this type.

Case 1 was a man of 70 who admitted that he wore his dentures only when going out. He had had a Billroth I operation, with a 4-cm.-diameter stoma, done one year earlier. He presented with intestinal obstruction, and a mass of orange-pith was removed from the lower ileum by enterotomy, but he died five days later.

Case 2 was a man of 36 with good teeth, who three years earlier had had a Polya gastrectomy converted to a Billroth I, together with vagotomy. His gastro-duodenal stoma was

3.5 cm. in diameter. He presented with obstruction following his meal of cod-roe and chips. At operation the food masses in the lower ileum were milked into the caecum. The appendix was removed.

Case 3 was a woman of 57 with adequate teeth, who had had a Polya gastrectomy done seven years earlier. A pre-operative diagnosis of acute appendicitis was made, but at operation a mass of orange-pith was found in the lower ileum. It was milked downwards and removed through the base of the amputated appendix.

Case 4 was a woman of 75 with very deficient teeth who had had no previous operation. Acute appendicitis was diagnosed, but at operation there was a mass of orange-pith in the lower ileum. It was removed as in Case 3. These last three patients have recovered.

If the obstructing bolus can be milked into the caecum it is probably unnecessary to remove it, but when an incision has been made in the right iliac fossa it is desirable to remove the appendix. Finally, we should warn the edentulous to eschew the orange.—We are, etc.,

M. R. Madigan.
S. L. Strange.

Whittington Hospital,
London.

Pubopenile Testis

Sir,—I was rather surprised to see the memorandum by Dr. C. D. Collins (*Journal*, August 22, p. 225) reporting two cases of pubopenile testis and stating that the type is rare. Many more cases must be seen all over the world, and particularly by surgeons in my country, than have been put on record.

In 1953 I was brought an Ishan boy, aged 1 year, complaining of a swelling on the dorsum of his penis. On examination, he had a normally situated testis on the right while the left side of scrotum was empty. At operation it was quite easy to free the well-developed, ectopic testis on the dorsum of the penis, near its root (see photograph), and transfer it into the scrotum.—I am, etc.,

Xto G. Okojie.

Zuma Memorial Hospital,
Irrua, Nigeria.

New Sulphonamides

Sir,—There have been two schools of thought concerning sulphonamides in the treatment of dysentery. One has favoured soluble forms, the other insoluble. Whichever type is used, the frequent dosage and large number of tablets required constitute a nuisance, particularly when, as in the outbreak described below, the population consists of senile psychotics. The administrative problem becomes even more acute in the setting of a severe shortage of nurses, characteristic of mental hospitals.

The outbreak occurred in a ward of 52 patients. The illness was characterized by a sudden onset of loose, offensive stools, colic, and pyrexia in the range 99–101° F. (37.2–38.3° C.). The first three patients who fell ill in the first 10 days received no specific treatment other than bed rest and a light diet. They may be regarded as a small (very unstatistical) control group. They had violent diarrhoea on some days, hardly any on others. None was very ill.

More patients became affected, and *Shigella flexneri* Type X was isolated. Laboratory investigation showed that the organism was sensitive to "sulphatriad" +++, sulphaguanidine ++, phthalylsulphathiazole +++, chloramphenicol +++, sulphamethoxypyridazine ++, sulphadimidine ++. It was decided to treat the whole ward prophylactically. First, stools, or, failing this, rectal swabs, were obtained from the whole ward, to detect possible carriers. The administrative problem of medication was met by choosing sulphamethoxypyridazine (see *Journal*, September 19, p. 482), for, though it scored but ++ on sensitivity test, it could be given at a dosage of 1 g. (2 tablets) stat., followed by 0.5 g. (1 tablet) daily.

The day following the start of prophylaxis, a pathological report revealed a symptomless carrier, who in fact was a ward-kitchen worker. Despite her late identification, no more cases occurred. An arbitrary 7 days' prophylaxis course had been decided on, but an episode of loose stools in a new patient on the eighth day of treatment led to an extension of 4 days. This patient, however, had only an upset of a few hours and her stools were negative.

Treatment.—(1) *Prophylactic:* sulphamethoxypyridazine, 1 g. stat., 0.5 g. daily for 11 days. (2) *Carrier* as (1). (3) *Therapeutic:* (*a*) Three cases were positive for *Shigella flexneri* Type X. One was treated with phthalylsulphathiazole 2 g. stat., 1 g. four-hourly, for 5 days. Two were treated as in (1) above, for 5 days only, however. (*b*) Three cases were clinically dysenteric before mass treatment began, but their stools were negative for pathogens. Treatment as in (1).

Clinical Assessment: The patient treated with phthalylsulphathiazole had no loose stools in 3 days and was symptomatically better. The patients treated with sulphamethoxypyridazine had no loose stools in 2 days and were well again. These cases may be compared with the tiny control group (*vide supra*). Group (3) (*b*) responded like (3) (*a*).

Toxicity: Out of the 52 treated patients, only 1 showed a toxic reaction. This was a patient with chronic eczematous dermatitis, who was in the prophylactic group. On the eleventh and last day of treatment a pleomorphic, widespread, morbilliform, urticarial, and scarlatiniform rash appeared. The patient became febrile for 2 days (99° F.—37.2° C.); the rash began fading on the third day; on the fifth it had gone. The only treatment was a switch from chlorpheniramine maleate ("piriton") 4 mg. t.d.s., which the patient had already been on for her original skin complaint, to promethazine hydrochloride ("phenergan") 25 mg. t.d.s. on the first day of the rash.

Follow-up: The usual quota of stools — that is, 3 consecutive negative stools—was now obtained to clear the ward at the end of treatment. All stools were negative. Stools from patients originally positive were checked weekly for 6 weeks. These were all negative.

It is considered that a potentially large outbreak of Flexner Type X dysentery was aborted by prophylactic use of sulphamethoxypyridazine, which proved to be an effective, easily administered agent both for prophylaxis and treatment.

I wish to acknowledge the assistance of Dr. W. W. Kay and Dr. I. H. MacLean, Mental Hospitals Group Laboratory, West Park Hospital, and Messrs. Parke, Davis & Co. for a free supply of "midicel" (sulphamethoxypyridazine) and for help and advice.—I am, etc.,

A. Crowcroft.

West Park Hospital,
Epsom.

Dilatation and Curettage

SIR,—In every gynaecological operation theatre the "list" ends with a number of "D. and C.s" with or without cautery or erosions or tubal insufflation. Leaving aside the fact that a certain proportion of these "erosions" are either ectropions of the columnar epithelium of the cervical canal or are innocuous, uninfected, and often transient, and as such are not properly treated by massive coagulations, and after allowing for all the proper indications for dilatation and endometrial curettage, we may consider the possible unfortunate effects which may result from their injudicious performance.

Dilatation.—Both this and curettage are sometimes done by the strong man technique: go on dilating forcibly till the circular fibres are ruptured and their ends widely separated, leaving ultimately a zone of cicatrix or an incompetent internal os tending to allow subsequent pregnancies to terminate by bulging and bursting through the gap during the early months.

Curettage.—Again sometimes a vicious scraping which can lead to synechial adhesions between contiguous portions of exposed myometrium, again leading to sterility or early abortion. Let us leave out the occasions where the uterine wall is perforated, usually a matter of little consequence, and the far worse indiscretions and disasters which are not unknown. On the other hand every gynaecologist will have had to re-do a D. and C. for an incomplete abortion where his house-surgeon by over-caution has merely dilated and curetted the cervical canal.

There are many and excellent indications for these simple and time-honoured lines of treatment, but my plea is that the selection of cases and the method of performance require more discretion than is often given to them.—I am, etc.,

East Grinstead. W. C. SPACKMAN.

Toxic Epidermal Necrolysis

SIR,—I was interested to read Dr. J. V. F. Catto's article reporting this condition occurring for the first time in a child (*Journal*, September 26, p. 544). Within 24 hours of reading this I was confronted with an almost identical case.

A girl, aged 3 years, who had had a mild eczema of the face at 2 months of age, attended hospital on September 26, with the history of having grazed her left knee 10 days previously. Two days later she visited her uncle, whom I was treating for persistent impetigo of the chin with neomycin ointment, and 48 hours later she had an impetigo of the grazed area. She vomited three or four times. Her doctor treated her with "vioform" and hydrocortisone locally, tetracycline suspension 250 mg. twice daily for four days, promethazine hydrochloride 5 mg. twice daily, but the condition spread on the left leg and to the face round the mouth. I then saw the child on September 26 and ordered neomycin ointment as a local application applied three times a day.

Two days later I saw the child again at her home. She was lethargic, looked ill, and had a temperature of 100° F. (37.8° C.) with a pulse rate of 100 and respirations 20. She was admitted to hospital the next day (September 29). The lesions of impetigo were still present on the face and left leg. Large areas of skin on the back of the neck, chest, and right flank, as well as most of the face and the eyelids, were red, swollen, and extremely tender to touch. The child would not lie on her back because of the painful skin. Large areas of skin had lost the superficial covering, leaving raw, moist, red, oozing areas similar to scalds; on these areas were scattered large flaccid bullae. Nikolsky's sign was positive on the red, tender areas of skin. There was no tonsillitis or other gross abnormality found on physical examination.

A swab from the impetiginous lesions grew *Staphylococcus aureus* resistant to penicillin and tetracycline but sensitive to streptomycin and chloramphenicol. She was treated with chloramphenicol palmitate suspension 125 mg. three times daily, and the temperature returned to normal in 24 hours; the chloramphenicol was discontinued after four days, when the skin had improved enormously. The only local treatment was dibromopropamidine cream *B.N.F.* applied three times daily to the impetiginous and denuded areas. She was discharged from hospital on the ninth day with the skin appearances quite normal; the denuded areas were healed and almost indistinguishable from the surrounding skin except for slight erythema.

No drugs other than those mentioned above had been given. She was not treated with corticosteroid as in Dr. Catto's case.—I am, etc.,

Bristol, 8. CLIFFORD EVANS.

Steely Eyes and Pain

SIR,—Returning from holiday, I used your excellent journal to review what progress the medical profession had been able to make in my absence.

The annotation on steely eyes and pain (*Journal*, September 12, p. 418) closes with a request to know if medical men pay any attention to colour of eyes when assessing patients with complaints of pain. This has been, for years, one of my minor points of which to make note, and it has been my impression that dark brown eyes, low threshold, and perhaps over-reaction have tended to go together. In ordinary medical illnesses, standard pain stimuli are not easy to find or use, though I did—particularly before 1948, when time seemed to go further—attempt a variety of tests.

As your annotation suggests, I also wondered if a Mediterranean strain might imply increased excitability, which is—or can be—a different thing from low threshold. My out-patient department includes quite a number of people whose ancestors arose round the Mediterranean.

In addition to brown eyes, retinal pigmentation may be present, and so may dark hair, and these characteristics may also be used in assessing categories. I believe also that brown-eyedness may be a genetically dominant character, but I suppose may be inherited independently of other characteristics, so that its exact significance needs, perhaps, more care in assessing. It is an interesting point in clinical consideration of pigmentation that eyebrows quite often stay black several years after the hair of the head has become white. My barber thinks that this is more likely to happen if the eyebrows are not trimmed, and I have some personal experimental evidence to support this idea.—I am, etc.,

Hove, Sussex. W. A. BOURNE.

The Customary Fee

SIR,—Mr. W. R. Smith's letter (*Journal*, September 26, p. 583) raises a most pertinent question of payment between medical colleagues. I was taught that, as a matter of courtesy, fees were waived when one doctor treated another, and I understood that this courtesy was usually extended to the wives and children also. (I later discovered that certain eminent consultants did charge fees to other doctors, and not always reduced fees by

any means, but I doubt if the habit was widespread, particularly before the last war.) In order to compensate for this loss of income, which in the case of some popular consultants could be considerable, the general practitioner referred private cases to his obliging colleagues.

I am sure that the majority of consultants still follow this custom, but the advent of the N.H.S. has resulted in the virtual disappearance of private practice, so that their services to their fellows and their families go unrewarded, and in some cases, I regret to say, seem to be quite unappreciated. When it is considered how much extra attention a doctor is prepared to give to a suffering colleague, or his family, not to mention the added anxiety and responsibility such attention entails, it is hardly surprising that some consultants, such as the one mentioned by your correspondent, now charge fees for their services. I am sure, however, that the practice is still uncommon.

Surely one sensible answer to this problem is for every doctor—unless he is without any conscience in the matter—to take out an insurance policy against illness on behalf of himself and family. Thus for a very modest annual payment he can at once largely meet the cost of private hospital treatment and ensure that the attentions of his colleagues do not go unrewarded. The Hospital Service Plan is such a scheme which should particularly commend itself to the medical profession, although in common with other similar insurances it makes no provision for normal maternity care.—I am, etc.,

Rochester, Kent. STANLEY W. WRIGHT.

SIR,—"Another Retired G.P." (*Journal*, October 10, p. 695) has been more fortunate than I have been in his relations with consultants. This was my recent experience in the south of England: my teen-age daughter required an appendicectomy; the surgeon charged me 75 guineas and the anaesthetist charged me 7 guineas. The accounts were not sent in ignorance.

As Dr. Bouché says (p. 695), the principle involved is the important thing, but I think that these fees could fairly be regarded as heavy. The stated opinion of the B.M.A. is that there is nothing contrary to ethics in this practice. I think it is deplorable.

I offered a fee to the G.P. concerned. He refused it. I think he was rather offended by my offer.—I am, etc.,

RETIRED M.O.H.

POINTS FROM LETTERS

Inoculation Recording by Tattooing

Dr. C. T. PIPER (Adelaide) writes: I have read with great interest the article by Mr. Norman Lake entitled "Inoculation Recording by Tattooing" (*Journal*, August 8, p. 141). . . . I agree that this should be an international code, and I agree that it should be standardized and in one particular spot on the body. The principal objection, of course, is that if this thing is compulsory it constitutes a sanction of a governmental assault on the body of its subject, rendering him subject to identification and also to branding in various ways, and it can be quite visualized that this could be abused in the wrong sort of system. I should think that we have all seen the people with their P.O.W. numbers tattooed to their forearms who have come out of Nazi Germany, and I can think of nothing more objectionable than being branded in this way. But I do agree that it is most desirable that this should be done, and that particularly any evidence of hypersensitivity should be recorded in a way that will save the patient from being destroyed by repetition of similar treatment.

Obituary

J. W. A. HUNTER, M.D., F.R.C.O.G.

Dr. J. W. A. Hunter died in Manchester on October 10 at the age of 65. His final illness was short and he had retired only in August, on reaching the age limit, from his appointment as consultant obstetrician and gynaecologist to St. Mary's Hospitals for Women and Children, Manchester.

John William Alexander Hunter was born at Derby of a family originating in Aberdeenshire. He went to Edinburgh University for his medical training, but this was interrupted by the outbreak of the first world war, in which he served as a combatant in the Royal Field Artillery from 1914 to 1918. Returning to Edinburgh, he graduated M.B., Ch.B. with honours in 1921. He proceeded M.D. in 1932. After a term as house-surgeon at the Royal Infirmary, he filled a similar post at the Simpson Maternity Hospital, Edinburgh. His association with Manchester began in 1923 when he was appointed registrar and obstetric surgeon to St. Mary's Hospitals. Here he came particularly under the influence of Dr. W. E. Fothergill. Later he was elected to the visiting staffs of the Manchester Northern Hospital, the Jewish Hospital, and the Withington Hospital. He was appointed demonstrator in obstetrics and gynaecology in the Victoria University in 1927. Eventually he returned to St. Mary's Hospitals as consultant obstetrician and gynaecologist. Hunter was a foundation member of the Royal College of Obstetricians and Gynaecologists and was elected to its Fellowship in 1938. He was president of the North of England Obstetrical and Gynaecological Society in 1951, and he made many contributions to the literature of his specialty in this and other journals. He had been a member of the B.M.A. for 30 years.

W. I. C. M. writes: Hunter never spared himself, despite a deterioration in his health which had been obvious to his friends for some years. His final illness was mercifully short. His work became well known in this country and abroad. His many publications included contributions to British and American literature, and his well-known film of the Fothergill operation was originally presented by invitation to the International Conference of Obstetrics and Gynaecology at Paris in 1952. Of the many distinctions which he received, he was proudest of his presidency of the North of England Obstetrical and Gynaecological Society. His presidential address on the medical references in Shakespeare was a tribute to his meticulous scholarship in medicine and in literature.

Precision and attention to detail were Hunter's chief characteristics in all spheres of activity. His gynaecological surgery particularly exemplified this. Indeed, his registrars and house-surgeons used to speak admiringly of his "Bond Street operating." His obstetrical judgment is legendary. He was a most respected teacher, both of medical students and of midwives. The obituary notice of him in the *Guardian* (October 12) was followed on the succeeding day by a tribute expressed most touchingly in a letter from a senior midwife in the city.

His passing is mourned not only by his old students but by thousands of Manchester women, while the recipients of his private generosity will remember him with gratitude. It was characteristic of the man that he kept such matters hidden as much as possible. His embarrassment was almost comical when it came to light that he was a financial contributor to the successful Everest expedition. This did not surprise his friends, for he was in his day a notable mountaineer. His other interests included motoring, flying, and, above all, fishing. Those best qualified say that he applied to the killing of a salmon those very qualities of meticulous care which he used in his surgery. In person he was rather below the middle height. His physique was wiry rather than robust. He was basically rather a shy and

sensitive person who took refuge behind a brusque and even pugnacious manner. He had great qualities of firmness, perhaps even obstinacy on occasion. A bachelor, he is survived by a sister, to whom his many friends offer condolences.

T. S. NELSON, M.A., B.M., B.Ch., F.R.C.P.

Dr. T. S. Nelson, a well-known authority on chest diseases, formerly senior physician to the West Middlesex County Hospital, and consultant physician to St. George's Hospital and the Brompton Hospital, London, died in a London hospital on October 14. He was 70 years of age.

Thomas Sydney Nelson was born in Kensington in 1889, the son of S. H. Nelson. He was educated at King's School, Canterbury, where he was a foundation scholar, and from there he went up to University College, Oxford, and took his B.A. in 1912. He was later elected Radcliffe travelling fellow. He received his clinical training at St. George's Hospital and qualified L.M.S.S.A. in 1914. The first world war then intervened in his career and he served in France and Italy as a captain in the R.A.M.C. For three years he was regimental medical officer with the 14th Brigade, Royal Horse Artillery.

Returning to St. George's after the war, Nelson took his conjoint diploma in 1920 and was in turn house-physician and house-surgeon at his teaching hospital. He graduated B.M., B.Ch. in 1921, and in the same year proceeded M.A. He obtained the M.R.C.P. in 1922 and was elected F.R.C.P. in 1934. He was for a time assistant tuberculosis officer for the City of Bristol before being appointed to the medical staff of St. George's and of the Brompton Hospital for Diseases of the Chest. He also acted as physician to the St. Marylebone Dispensary and was consulting physician for diseases of the respiratory tract to the Ministry of Pensions. He was later appointed physician to the West Middlesex County Hospital and also physician to the Teddington Memorial and Brentford Hospitals and the Upton Hospital, Slough.

Dr. Nelson married Dr. Grace M. Beaven, also a member of the medical profession, who survives him and to whom we tender our sympathy.

J. B. FERGUSON WILSON, M.S., F.R.C.S.

Mr. J. B. Ferguson Wilson, formerly consulting orthopaedic surgeon to the United Sheffield Hospitals, died at his home at Sheffield on June 24. He was 76 years of age.

John Black Ferguson Wilson was born at West Derby, Lancashire, on May 14, 1883, and was educated at Leeds Grammar School and at Leeds University. After a brilliant undergraduate career at the university and at the London Hospital, where he received his clinical training, he qualified in 1906 and obtained the London degrees of M.B., B.S. in the following year. He then held house appointments at the General Infirmary at Leeds in 1907 and at Sheffield Royal Hospital from 1908 to 1912. In the latter year he was appointed honorary assistant surgeon to the Royal Hospital, which he continued to serve until his retirement in 1943. He proceeded to the M.S. in 1914, having obtained the Fellowship of the Royal College of Surgeons of England in 1910.

We are indebted to three of his colleagues for the following appreciation:

Early in his surgical career Mr. J. B. Ferguson Wilson was attracted to orthopaedic surgery, and by the end of the first world war he was taking a special interest in it, which increased throughout his surgical career, though he never ceased to be a general surgeon. At the invitation of Sir Robert Jones he joined the British Orthopaedic Association shortly after its foundation, and maintained the greatest interest in it till his retirement, seldom missing any of its meetings. Although not by nature an experimenter, in many respects he was ahead of his time: for example, he was one of the first to use caudal block anaesthesia regularly and was amongst the pioneers of punch prostatectomy. Extremely widely read, he early became an authority on the literature of surgery, and on retirement in 1943 he presented almost the whole of his collection of books to the hospital library. As a surgeon he was sound in diagnosis and conservative in treatment. Acknowledged by his colleagues to be a surgeon of the first rank, he never received the wider recognition which his talents merited, as he shrank from any form of publicity, and from publishing. His great diffidence and retiring disposition made him a difficult man to know intimately, but such was his character and disposition that he was held in affectionate regard and esteem by all his colleagues, and everyone who knew him. To the few who were privileged to enjoy his intimate friendship he displayed a munificent hospitality. His leisure pursuits were classical music, of which he had a fine collection of records, and, curiously enough, the cinema. Ferguson Wilson never married. To his brother we offer the sympathy of his professional brethren.

A. P. MITCHELL, M.D., Ch.M., F.R.C.S.Ed.

Mr. A. P. Mitchell, formerly surgeon to Leith Hospital, died at Edinburgh on September 2. He was 74 years of age.

Alexander Philp Mitchell was born in Edinburgh. He was educated at the Royal High School in his native city, and received his medical training at Edinburgh University, where he had a distinguished undergraduate career and won the McCunn scholarship in surgery. He graduated M.B., Ch.B. in 1907. After graduation he held resident appointments on the medical and surgical sides of the Edinburgh Royal Infirmary, and as house-physician at the Royal Hospital for Sick Children. He proceeded M.D. in 1909, became a Fellow of the Royal College of Surgeons of Edinburgh in 1912, and obtained the degree of Ch.M. of Edinburgh University in 1913, with a gold medal for his thesis. The B.M.A. awarded Mitchell a research scholarship in 1911 and the Ernest Hart Memorial Scholarship in 1912. For some five years he acted as private assistant to the late Sir Harold Stiles.

During the first world war Mitchell was for a time interim assistant surgeon at the Royal Hospital for Sick Children, and as a captain in the R.A.M.C. he served in Scotland on the staffs of Bangour and Craigleith Hospitals, where he obtained a wide experience in orthopaedic and traumatic surgery, which remained one of his chief interests. In the earlier part of his career Mitchell did much work, and contributed to the literature, on surgical tuberculosis in children, which at that time was so prevalent in Scotland.

In 1925 Mitchell was appointed an assistant surgeon at Leith Hospital, where he was successively surgeon to the children's wing and to a general surgical department, and there he served his community until his retirement from the hospital service. In addition to his clinical work, he was much in demand as a consultant and as an assessor in compensation and medico-legal cases, where his experience and dignified bearing made him a valued adviser and impressive witness. The width of his interests is exemplified by his work at Hartwood Asylum and Associated Hospitals, where late in his career he investigated and operated on cases requiring leucotomy.

Mitchell was for a time an elder in the Church of Scotland. He was a connoisseur of art, and keen on photography. On retirement from his hospital appointments at the age limit he was still youthful in appearance and spirit. He was particularly fortunate in being surrounded by his family, to whom he gave so much affectionate guidance and care. He was something of an individualist, as so many surgeons tend to be, but he was a great lover

of children, flowers, and the beauties of nature. Our heartfelt sympathy goes out to his devoted wife and young family, two sons and two daughters, in their loss.—J. R. J. C.

B. A. HOOGEWERF, L.M.S.S.A.

Dr. B. A. Hoogewerf, a well-known practitioner in St. Paul's Cray and St. Mary Cray, Kent, died at his home in St. Paul's Cray on September 28. He was 60 years of age.

Bernard Albert Hoogewerf was born in India on June 6, 1899. He studied medicine at Madras University, where he qualified in 1921, and later, from 1936 to 1938, at King's College Hospital, London, from which he took the L.M.S.S.A. in 1937. He served in the Indian Medical Service from 1921 until its end in 1947, and was mentioned in dispatches for services in action. In 1940 he was appointed medical officer, ordnance and munition factories, Kirkee, Bombay, with one dispensary. By 1947 he had built up a comprehensive medical service with a main hospital of 80 beds, a detention hospital of 20 beds, five dispensaries, a child-welfare centre, and a tuberculosis clinic to care for 25.000 Indian employees and their families.

Leaving India in 1947 Hoogewerf entered general practice in St. Mary Cray. With the building of an L.C.C. housing estate in the neighbourhood his work rapidly increased, but in his large practice he always retained a keen interest in the needs of his patients. He also became deeply interested in medical organization. He was a past-chairman of the Bromley Division and a past-president of the Kent Branch of the British Medical Association, and a member of the group medical committee of the Orpington and Sevenoaks Hospital Management Committee. He was also a member of the local medical committee for Kent. In co-operation with Group Captain G. L. Cheshire he founded, and was chairman of, St. Cecilia's Home for the Sick at Bromley. He was chairman of the St. Paul's Cray health group, membership of which is open to general practitioners, consultants, and those in all branches of ancillary medical work. It meets monthly and is addressed by visiting specialists. A devout Roman Catholic, he served on the committee of the Guild of SS. Luke, Cosmos, and Damian. A short time before his death, which was relatively unexpected, he felt that his health would not allow him to serve adequately the committees of which he was a member, and he resigned from them all forthwith.

Throughout his career Mrs. Hoogewerf supported her husband in all his activities. He leaves a son in the Colonial Medical Service and two daughters, one recently qualified in medicine. Their loss is very great and is shared by his many patients, who have lost a kind and hard-working friend, one who would wish nothing more to be said of himself than that he spent his life in the service of God. —G. A. G.

J. L. C. writes: It is distressing indeed to record the death of Bernard A. Hoogewerf, who for the last ten years gave such devoted service in the district of St. Paul's Cray. During the last war he worked untiringly in organizing a large hospital attached to the munitions factory in India, and he retired from the I.M.S. with the rank of major. He brought the same dedicated devotion to his practice in St. Mary Cray and St. Paul's Cray, where he was a much-loved and respected physician. He took an active part in the life of the local Roman Catholic churches, and his efforts were instrumental in the founding of the Roman Catholic Manorfields School at St. Paul's Cray. His religious life was exemplary and an inspiration to many. At the Requiem Mass the church was filled to capacity and the crowd stretched beyond the doors. His personal qualities were such that his friends felt honoured by his friendship. He was a loyal colleague and brought to his patients not only his skill but also an understanding sympathy. His loss will be deeply regretted in wide circles, professional, religious, and social, and he will long be remembered by his fellow doctors, friends, and patients. Dr. Hoogewerf, in spite of his many activities, was a family man in the truest sense of the word and was devoted to his home life. To his widow, his son, and his daughters must be extended a very special sympathy in the loss of so loving a husband and so fine a father.

ROBERT TILBURY, M.R.C.S., L.R.C.P.

Dr. Robert Tilbury, who was in general practice at Peckham for many years, died at Putney Hospital on September 21 after a long illness. He was 85 years of age.

Robert Tilbury was born on March 25, 1874. He qualified from Guy's Hospital in 1901, and then served as a civil surgeon with the South African Field Force. Soon after his return to England he took over the practice of Dr. H. E. Cock in Peckham, where he remained until 1943, except for the period of his service as a lieutenant in the R.A.M.C. with the British Expeditionary Force in France in the first world war. He was chairman of the Camberwell Division of the B.M.A. from 1936 to 1939. He leaves a widow and two stepchildren.

G. E. G.-A. writes: Dr. Robert Tilbury fulfilled all that was best as the family physician and was very widely known and respected for his clinical acumen and professional integrity. He was a fine example of all that a Guy's man should be.

JOHN KIRK, M.B., F.R.C.S., F.R.C.S.Ed.

The obituary of Professor John Kirk was published in the *Journal* of October 10 (p. 698).

J. W. Dickson writes: The death of Professor John Kirk ended a friendship of twenty years. As his pupil, then as a very junior member of his department, and long after I had left the Middlesex, he befriended me and went out of his way to help. At a time of great personal sorrow he was a staunch and loyal friend. As a teacher of what he used to call "Barn Door Anatomy" he was exceptional. He combined a profound knowledge of topographical anatomy with a long experience of surgery. To be taught physiology by Samson Wright and anatomy by John Kirk was something for which many of us will be constantly grateful. For slackers he had no use, but for every one of his pupils he had a firm and kindly word, treating each one with courtesy and dignity which we little deserved.

One can truthfully say that no one ever had such a lucid teacher, so good a chief, or so true and unwavering a friend. He had Osler's *aequanimitas*, springing from a deep love of God and his fellow men. Some years ago he told us that two things had upheld him: the Christian faith and the love of a good wife. To her and to his family go our sympathy and affection.

W. S. GILMOUR, O.B.E., M.B., Ch.B.

The obituary of Dr. W. S. Gilmour was published on September 19 (p. 509).

Dr. Harley Williams writes: Your sympathetic obituary does not perhaps allow a full measure of originality to Santon Gilmour's survey work in tuberculosis. His inquiry in the British West Indies, in 1943 and 1944, was truly a pioneer labour. The Comptroller for Development and Welfare of these Colonies had suggested that their tuberculosis death rates were higher than in England. Verification and recommendations were clearly needed, and the Colonial Office sent Santon to the Caribbean, a substantial contribution towards the expenses being made by N.A.P.T., which also published his report. Santon Gilmour conducted the research single-handed, and produced an excellent summary of his findings. Death rates, especially among the aboriginal Indian and African populations, were

indeed higher than in Western Europe. To-day, the idea of such colonial surveys is no longer new, and field work is done with techniques not available to Santon Gilmour. But his West Indies investigation remains a striking personal effort.

Gilmour assumed no airs but those of a simple, ordinary person, and undiscerning people took that for fact. He was a man of considerable ability, and got his way through personal charm. It was impossible to quarrel with him, and these gifts were a part of his success in elucidating tuberculosis among simple people in Uganda, China, and Bermuda, where he made his last survey in 1950.

A colleague writes: As recently as July 8 last his fellow members of the Yorkshire Thoracic Society made Dr. W. Santon Gilmour a presentation on his retirement as president. On this social occasion, Hamlet's famous second line about Yorick was used to describe him: "A fellow of infinite jest, of most excellent fancy." Little did one guess then that the first line, "Alas, poor Yorick, I knew him well," could be quoted so soon. Knowing him since 1931, we frequently met *en famille*. "We tired the sun with talking and sent him down the sky." To his widow, Enid, and his son, Richard, our sympathy on his premature death is extended. Again one can appropriately quote from Cory's translation of the tribute paid by Callimachus on hearing of Heraclitus's death, "Still are thy pleasant voices thy Nightingales awake, for Death he taketh all away, but them he cannot take."

W. W. FRANCIS, M.D.

The obituary of Dr. W. W. Francis was published in the *Journal* of August 22 (p. 247).

Dr. A. R. Southwood (Adelaide) writes: May I add a sprig of Australian wattle to the tributes of Sir Arthur MacNalty and others? For Osler-worshippers the world over the name of Francis is as firmly linked with that of Osler as Boswell's is with Johnson's. What a great leader was Osler. With a facility given to few he infused into his writings his very soul; even those of us who knew Osler only through his writings have felt the warmth of his companionship. And Francis, through his lifelong devotion, has helped to keep alive the memory of his chief. The Osler library at McGill will always be a Mecca for doctors, but the kindly guidance of Francis will be missing now. Yet the influence of good men lives on: "There shall never be one lost good."

Medico-Legal

THE CORONER AND THE MEDICAL MISHAP

[From a Special Correspondent]

It is inevitable that many deaths occur in connexion with operative procedures. No surgical operation is quite free from risk, and the assessment of this is a big part of the surgeon's skill and experience. Desperate diseases need desperate remedies, and it is not right that the surgeon should have to justify in public his decisions in every case that goes wrong. At the same time, the public interest demands some sanction, other than the surgeon's conscience, for protection against ill-chosen or careless procedure.

Coroner's Duty

The coroner must make inquiry into all violent and unnatural deaths. The medical mishap comes under this heading, and in areas where there are many hospitals the coroner may often have to decide whether or not to hold an inquest. There are no exact statutory rules to guide him, and practice varies according to the individual coroner. Were an inquest held into every death following operation the surgeon would spend much of his valuable time in court, and public confidence would be undermined. The surgeon must be left free to do his work secure in the knowledge that he will not be exposed unnecessarily to public criticism.

It is not easy to formulate rules to guide the coroner in deciding whether to hold an inquest. It must again be emphasized that practice varies. However, the following principles seem to be generally accepted in deaths following surgical interference.

(1) Where operation is undertaken for serious disease, and is properly indicated and competently performed, no inquest will be held. This applies, for example, to a case of peritonitis following perforated peptic ulcer, or to the extensive resections for carcinoma with spread to adjacent viscera. In such cases nobody can forecast the degree of shock in the individual patient.

(2) Where there is allegation of neglect or incompetence leading to death, the coroner will hold an inquest. Most of such allegations prove to be unfounded, and public inquiry is valuable to vindicate the surgeon's actions.

(3) Where there has been a clear miscarriage of surgery, quite apart from the disease, an inquest must be held. Examples are an incompatible transfusion, a death solely due to anaesthesia, or a case in which both ureters were tied during a hysterectomy.

(4) Where it seems that the practitioner has gone beyond his powers an inquest is necessary. An example is the general practitioner who undertakes infrequent major abdominal surgery. This might not apply to the man who does his best in an emergency.

The value of the inquest in the last two categories is undoubted. In the former, dangers in familiar procedures can be publicized, and in the latter the publicity provides a needed sanction to restrain the incompetent or vain.

"Accident" or "Misadventure"

It is not necessary to sit with a jury in inquests on medical mishaps. The verdicts of "accident" or "misadventure" sometimes cause confusion. The terms are interchangeable and are entered in the same columns in the coroner's annual return. The verdict of "accident" is perhaps used more often, "misadventure" tending to be regarded as archaic. In any case, there is no significance in the choice of which verdict is recorded.

Illustrative Cases

Two recent cases illustrate unusual medical mishaps.

Heart Perforated by Catheter

A man aged 42 had a partial gastrectomy for a large gastric ulcer. This was followed by a biliary fistula, and two further operations were undertaken for its closure. His condition was actually improving, but it was necessary to feed him intravenously for the time being. The arm veins had become thrombosed as a result of previous intravenous medication, so the saphenous vein in the groin was selected. A polythene catheter was introduced and passed for 10 in. (25 cm.) so that it lay in the inferior vena cava. A knot was tied round the catheter at the incision end, and the catheter was secured to the saphenous vein by two turns of catgut. The remaining part of the catheter was fastened to the skin with plastic tapes. The catheter remained *in situ* for four days, and the patient moved freely in bed and was given bedpans during this time. After four days the patient complained of pain in the right scapula, and quickly collapsed and died. Necropsy showed haemopericardium

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due to perforation of the posterior wall of the right ventricle by the polythene catheter. It was considered that the catheter had crept inwards on the current of blood in the inferior vena cava.

Recording a verdict of death by misadventure, the coroner said it was a pure accident and that not the slightest blame attached to anyone. He asked the doctors to see that details were published in the medical press so that other doctors might be warned of the possibility (*Birmingham Post*, March 20).

Liver Torn by Biopsy Needle

A man aged 59 was known to have amyloidosis due to chronic nephritis. It was decided that liver biopsy was indicated to assess the degree of spread of amyloid disease. The puncture was made through the right flank. During the procedure the patient breathed, and the doctor felt the liver tissue tear against the needle. Immediate advice on the question of internal haemorrhage was sought, but the man's grave condition precluded operation. Transfusion was given, but he died. Necropsy showed a 6½-lb. (3-kg.) liver which was pallid, waxy, and firm. There was a 1½-in (3.7-cm.) ragged tear on the lateral surface, and fatal bleeding had come from this.

The coroner recorded "death by misadventure," and said to the doctor concerned, "I am quite satisfied you did everything quite properly" (*Yorkshire Post*, May 21).

Wrong Blood at Operation.—At an inquest in Southampton on a woman of 71, a senior registrar said that the patient had been given blood of the wrong group as a result of a last-minute change in the order of the operating list. Despite immediate remedial measures, the patient died of renal failure. The registrar was commended by the coroner for the frankness of his evidence.—*Daily Telegraph*, September 10.

Universities and Colleges

UNIVERSITY OF OXFORD

Dr. Geoffrey Rushworth has been elected to a lectureship in medicine at Jesus College.

UNIVERSITY OF ST. ANDREWS

At a graduation ceremonial on October 7 the degree of M.D. was conferred, with commendation, on I. H. Redhead.

UNIVERSITY OF GLASGOW

In the list of successful candidates (*Journal*, September 12, p. 439) upon whom the degrees of M.B., Ch.B. were conferred on July 4 R. L. C. Cumming should have been shown as receiving the degrees *with commendation*.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on October 8, with Sir James Paterson Ross, President, in the chair, Peter Beck (Wyggeston Boys' School, Leicester, and St. Mary's Hospital Medical School) was admitted as Macloghlin scholar. The Jenks scholarship was awarded to G. A. C. Welply, formerly of Epsom College and now at King's College Hospital Medical School.

Diplomas of Membership were granted to L. P. Connolly, K. S. A. Madgwick, and R. P. Golding.

Diplomas of Fellowship in the Faculty of Anaesthetists were granted as follows:

F. J. Davis, M. E. Tunstall, R. C. Brookes, Pamela M. Ordish, G. D. Parbrook, C. B. Franklin, J. S. Toner, M. M. Som, J. E. Briffa, J. Fraser-Jones, M. Levitt, Lorna Chippindale, M. J. Egginton, J. Greenan, N. Ahmed, H. I. A. Nisbet, U. Weerackody, Joan D. A. Casserley, M. Cooke, Lois R. Davidson, E. P. Fitton, D. R. Ball, E. D. L. Bennett, T. H. L. Bryson, L. C. Fernando, Phillida M. Frost, J. G. Morgan, J. Wilson, P. V. Cole, Margaret C. Holderness, P. F. Knight, F. Fisher, J. C. Stoddart.

Diplomas were granted, jointly with the Royal College of Physicians of London, as follows:

DIPLOMA IN OPHTHALMOLOGY.—Aung Than, T. L. F. Averill, K. L. Batten, M. J. A. Britten, W. H. Clarke, Anthea M. S. Connell, M. S. Dawood, A. Freedman, R. N. Ghosh, M. El S. Ibrahim, E. O. Jacobs, B. S. Jay, S. M. Kamaluddin, T. D. Leckie, R. D. Loudon, D. J. McAuliffe, J. von L. Malan, Khalida Naib, R. S. Nanjundaswamy, Jean A. Peachey, J. F. Pereira, R. J. Pyne, N. S. C. Rice, I. F. Robertson, P. V. Rycroft, M. O. Sheriff, S. M. Siddique, I. Singh, D. Staig, W. E. Staples, J. M. Straiton, F. F. Sullivan, R. P. Tandon, J. N. Taylor, Tha Khin, P. Wright.

DIPLOMA IN PHYSICAL MEDICINE.—J. R. Burrows, L. Koadlow, L. H. Truelove, P. K. B. White.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—S. H. Ali, D. P. Arya, J. Barnes, Hildegard Berkhahn, R. J. P. Blyth, E. G. Budiyappa, D. M. Devane, A. H. Dossal, M. Ehtishamuddin, P. Faridian Araghi, S. M. Faruque, M. D. Gol'ing, M. A. Halim, A. G. Harwood, M. F. Hasan, D. S. Hutton, P. N. Jha, J. S. Karcher, H. A. Khan, M. A. Khan, E. P. Lawrence, Wan-Yee Lo, M. M. Mehta, G. G. Meiland, F. W. Murphy, K. G. Patel, L. C. Patel, S. P. Rastogi, M. Raza, Hilary M. Rowson, I. B. Sardharwalla, G. S. Sethi, N. Z. Shaikh, A. S. Shera, A. B. Shrestha, J. A. Siddiqui, W. G. Strauss, C. R. Tribe, D. M. Wayte, H. W. Whittingham, D. N. Wysham, Lois R. Zimmerman.

SCOTTISH TRIPLE QUALIFICATION BOARD

The following candidates passed the final examinations of the board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow, and were granted the diploma of L.R.C.P.Ed., L.R.C.S.Ed., L.R.F.P.&S.Glas. in October: A. H. K. Brohi, W. E. St. C. Crosbie, Isabella Gal, Dezso Schachter, Istvan Varga-Toth, Bik-May Wai.

Vital Statistics

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available

	Week Ending Oct. 3	Week Ending Oct. 10
Acute Poliomyelitis		
London	1	6
Islington	0	2
Yorkshire North Riding	0	5
Middlesbrough C.B.	0	3
Meningococcal Infections		
Warwickshire	5	9
Birmingham C.B.	5	8
Dysentery		
Lancashire	100	115
Liverpool C.B.	19	22
Swinton and Pendlebury M.B.	41	11
Worsley U.D.	8	35
London	55	48
Wandsworth	3	10
Staffordshire	6	13
Bilston M.B.	3	10
Yorkshire East Riding	26	34
Kingston upon Hull C.B.	18	25
Yorkshire West Riding	88	92
Leeds C.B.	25	34
Thorne R.D.	5	13
Glamorganshire	5	18
Cardiff C.B.	1	13
Glasgow	222	172
Food-poisoning		
London	32	34
Wandsworth	5	10
Lancashire	76	72
Liverpool C.B.	21	24
Acute Infectious Encephalitis		
Durham	3	1
Gateshead C.B.	2	1
Cerebrospinal Fever		
Glasgow	16	4
Diarrhoea and Enteritis in Infants up to 2 Years		
Belfast C.B.	15	24
Dublin C.B.	31	37
Dublin County	3	8

Polio Vaccination

Of children under 16 in Great Britain, 70% have had at least two doses of poliomyelitis vaccine, and 40% of people aged 16–26 have done so, according to the Ministry of Health. Of expectant mothers, 346,000 have received two injections, and 15,000 one. The total numbers of doses so far issued are: British, 15,678,000; Salk, 21,715,000; total, 37,393,000.

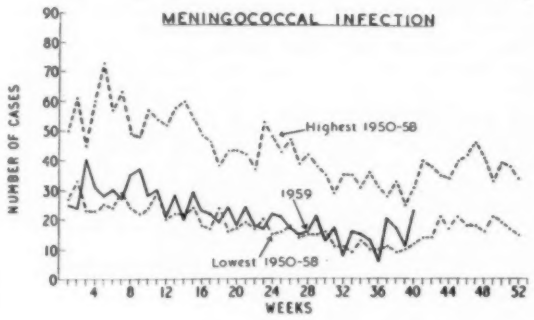
Eire in Second Quarter

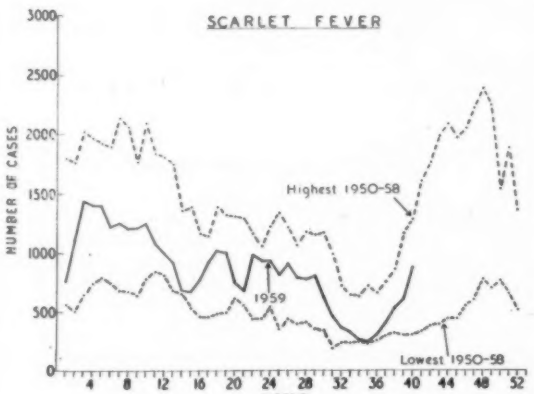
The birth rate for the second quarter of 1958 was 22.9 per 1,000 of the population and was 0.3 above the rate for the preceding second quarter. The infant mortality rate was 35 per 1,000 registered births, and the neonatal death rate was 24; these rates were, respectively, 1 below and 1 above the rate for the June quarter of 1958. The general death rate was 13.5 per 1,000 population, being 0.9 above the rate for the preceding second quarter, and was 1.2 above the average of the five preceding June quarters.

Deaths from tuberculosis numbered 117 for respiratory and 22 for other forms, and these deaths were 29 and 6, respectively, fewer than in the second quarter of 1958. The deaths from the principal infectious diseases included 353 from influenza, 5 from measles, 4 from whooping-cough, and 1 from diphtheria; 229 deaths were attributed to violence, and of these 48 were due to motor-vehicle accidents.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 3** (No. 39) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	2	2	0	0		2	0	0	0	
Dysentery	503	55	305	8	3	433	64	161	5	4
Encephalitis, acute	5	0		0		3	0		0	
Enteric fever: Typhoid	5	1	0	1	1	6	1	0	1	
Enteric fever: Paratyphoid	7	0	0	0	18 (B)	5	2	0	0	4(B)
Food-poisoning	269	32	30	1		347	52	22	2	
Infective enteritis or diarrhoea under 2 years				20	39				24	53
Measles*	794	26	12	18	31	1,621	120	19	4	55
Meningococcal infection	11	0	21	1		10	1	10	2	2
Ophthalmia neonatorum	19	1	7	0		25	3	3	0	
Pneumonia†	174	11	131	4	3	154	7	96	0	1
Poliomyelitis, acute: Paralytic	23	1	0	1		54	6	27	1	5
Poliomyelitis, acute: Non-paralytic	11	0	0			41	4			
Puerperal fever§	195	35	21	2		221	30	11	0	
Scarlet fever	605	55	109	14	28	543	42	72	17	18
Tuberculosis: Respiratory	365	41	56	20		465	52	84	21	
Tuberculosis: Non-respiratory	51	6	5	1		66	5	9	4	
Whooping-cough	639	37	92	11	16	671	41	68	51	37

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	1	0	0	0	0	0	0	0	0	0
Dysentery	1	0		0		1	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	9	0	1	0	1	4	0	0	0	0
Influenza	5	0	0	0	0	4	0	1	0	0
Measles		0	0	0			0	0	0	0
Meningococcal infection		0	0				1	0		
Pneumonia	320	25	23	10	7	304	18	10		4
Poliomyelitis, acute	1	0		0	0	2	0		1	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis: Respiratory	60	5	2	2	1	63	6	4	2	3
Tuberculosis: Non-respiratory		0	2	0	0		2	0	0	0
Whooping-cough	1	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	286	29	17	8	9	265	33	21	3	8
Deaths (excluding stillbirths)	8,255	617	502	111	143	7,978	663	489	100	133
LIVE BIRTHS	14,542	1197	1075	275	428	14,097	1192	962	225	361
STILLBIRTHS	272	23	25			304	21	17		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

New Medical Research Council Members

The Committee of Privy Council for Medical Research, after consultation with the Medical Research Council and with the President of the Royal Society, has appointed Professor A. L. Hodgkin, F.R.S. (Royal Society research professor, Cambridge University), and Professor R. Milnes Walker (professor of surgery, Bristol University) to be members of the Medical Research Council from October 1 in succession to Professor R. C. Garry and Mr. H. J. Seddon. The committee has also recently appointed Sir Hugh Linstead as the House of Commons member of the council in succession to the late Richard Fort.

Royal College of Obstetricians and Gynaecologists

The president, Professor A. M. Claye, who presided over the annual dinner of the Royal College of Obstetricians and Gynaecologists at the Dorchester Hotel on October 16, gave some news of the progress being made in the building of the College's new premises in Regent's Park. It would be roofed in the new year and completed by February 28. The opening ceremony would be on July 13. Professor Claye promised to tell members who was to perform the opening ceremony as soon as this was known—probably some time early in the new year. There would have to be another appeal for funds before next July, he said, since the high cost of maintaining and running the new building had to be faced. Lord Twining proposed the health of the College, and, as colonial governor, stressed the influence the College had, and could have in the future, on teaching standards in the "emergent countries." Mr. J. Bruce Dewar gave the toast of the guests. In humorous vein, he suggested that the College was behindhand in gaining publicity. Could not some programme such as "Your Wife in Their Hands" be put on the television, he asked? Lord Moynihan, the president's cousin, replied for the guests.

Westminster Hospital

The Old Students' dinner was held at the Criterion Restaurant on October 19 under the chairmanship of Sir Stanford Cade. It differed from most such functions in being less formal than usual—black tie and only two after-dinner speeches, much appreciated innovations. Sir Stanford Cade, whose association with the hospital stretches back 43 years and who is retiring shortly, proposed the toast to the hospital and medical school. In reply, Dr. Peter Kerley recalled what the hospital owed to Sir Stanford, a penniless refugee from Belgium with no English when he first came to them. Afterwards the company rose to their feet to acclaim him.

Leverhume Research Awards

Applications are invited for research fellowships and grants, and should be made on Form "F," obtainable from the secretary, Leverhulme Research Awards, St. Bridget's House, Bridewell Place, London, E.C.4.

These awards, for up to two years, are intended for senior workers and are normally limited to British-born subjects resident in the United Kingdom. Preference will be given to research subjects for which adequate provision is not already made. The closing date is December 31, 1959. Results will be announced in May and the awards will normally date from September 1, 1960.

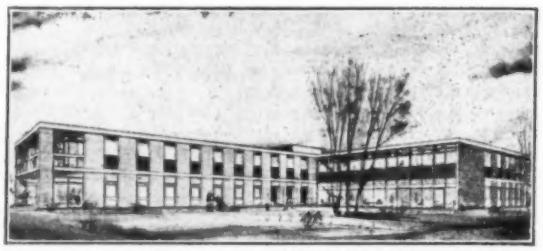
Rheumatology Conference at Istanbul

The Fourth European Rheumatology Congress was held at Istanbul from September 28 to October 1.

There were over 400 medical delegates and 200 associates. Some 120 members travelled by ship from Marseilles or Genoa via Naples and Athens and continued to use the ship as a floating hotel during the congress. Some considerable concern was shown over the danger of steroids being "served over the counter" in many countries, and the way in which they could easily be obtained without prescription even where medical prescription was officially required. The Russians made an interesting claim that a virus of the Coxsackie group may well be a factor in conjunction with the streptococcus in rheumatic fever. A report of all papers given at the Congress will be published later. All participants agreed that they could not have received greater kindness and hospitality. The chairman of the Turkish committee was Professor Paykoe, and Professor Kocas was vice-chairman and secretary.

Forston Clinic

A new psychiatric treatment centre, the Forston Clinic, was opened at Herrison Hospital, Dorchester, on October 2, by the chairman of the Wessex Regional Hospital Board, Mr. P. Templeman.



[*Gollins, Melvin, Ward and partners*

The name of the unit, which is designed for 96 in-patients and has extensive out-patient facilities, has been chosen to commemorate Francis Brown's gift in 1832 of his mansion house and lands at Forston to the county of Dorset for the establishment of a retreat for the mentally ill.

R.A.F.'s Health

The Royal Air Force in its *Report on the Health of the Royal Air Force and Women's Services of the Royal Air Force for the Year 1956*—it is a year ahead of the Army—says that there was less sickness in both the men and the women's services in 1956 than in 1955. Among the men the incidence of venereal diseases fell markedly, while the overseas figure for malaria was the lowest since the reports began in 1918; infectious mononucleosis continued to increase; athletic sports were, as usual, the commonest cause of injury—26% of the total. Comparison between rates for men and women showed that those for respiratory and locomotor groups were twice as high, and those for the mental group and other diseases group three times as high, among the women as those for R.A.F. personnel.

Royal College of Surgeons (Eng.)

When the Council met on October 8, Professor M. A. Rushton was admitted as a co-opted member representing dental surgery. Professor R. S. Pilcher was admitted to the Court of Examiners; the Handcock Prize was presented to Dr. E. W. L. Fletcher, and a diploma of Fellowship was granted to Mr. P. J. Carter.

Birmingham University

Mr. G. Slaney has been appointed senior lecturer in surgery at the University, and the following appointments to lectureships have been made: Dr. June K. Lloyd (paediatrics and child health), Dr. P. W. Dykes (medical biochemistry and experimental pathology), and Dr. I. M. Leck (social medicine).

Liverpool University

Dr. J. C. Davis has been appointed senior lecturer in endocrine pathology from October 1.

University of St. Andrews

Dr. J. A. R. Lenman has been appointed to a senior lectureship in neurology in the department of medicine, Queen's College, Dundee, with effect from January 1, 1960.

Institute of Laryngology and Otology

Professor F. C. Ormrod vacated the chair of laryngology and otology in the University of London on September 30, and has been elected professor emeritus by the Senate.

Association of Clinical Biochemists

At the sixth annual general meeting of the Association held at the Royal College of Surgeons, London, on October 3, the following officers were elected:

President: Dr. C. P. Stewart; *chairman:* Dr. A. L. Latner; *hon. treasurer:* Dr. J. H. Wilkinson; *hon. secretary:* Dr. A. L. Tárnoky.

B.M.J. Index

The half-yearly indexes to Volume I of the *Journal* and the *Supplement* for 1959 are now being sent to members who receive them regularly and to subscribers. Members who have not previously asked for the indexes to be sent regularly to them can obtain copies, post free, on application to the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1; those wishing to receive the indexes regularly should mention this.

COMING EVENTS

Association of Industrial Medical Officers.—The 88th meeting will be held at the Royal College of Surgeons, London, and King's College Hospital, S.E.5, on October 30 and 31. Details from the secretary, 47, Lincoln's Inn Fields, London, W.C.2.

Abortion Law Reform Association.—Annual general meeting, October 28, 6.30 p.m., Caxton Hall, Westminster, S.W.1, followed by public meeting. Speakers: Professor W. C. W. Nixon and Miss D. M. Kerslake, "Safety Aspects of Medical Termination."

Bradshaw Lecture.—Dr. Alan Kekwick: "On Adiposity," November 5, 5 p.m., Royal College of Physicians, Pall Mall East, London, S.W.1.

Sheffield Medical School Old Students' Association.—Annual dinner, Firth Hall, Western Bank, Sheffield, 10, November 7, 6.30 p.m. Details from the Secretary, c/o Department of Pathology, The University, Sheffield, 10.

Royal Medico-Psychological Association.—The 34th Maudsley Lecture, "Emergent Patterns of the Pathology of Mental Disease," by Professor Alfred Meyer, emeritus professor of neuropathology, University of London, 2.15 p.m., November 12, at the Royal Society of Medicine, Barnes Hall, 1, Wimpole Street, London, W.1. Admission without ticket.

West Riding Edinburgh Graduates Association.—Annual dinner, November 12. Details from Mr. J. S. Davidson, 33, Manor Row, Bradford, 1.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are available from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Journal of Ophthalmology.—Issued monthly (£6 annually). The new issue (Vol. 43, No. 8) includes:

Strabismus, Anisometropia, and Amblyopia. C. I. Phillips.
Measurement of Eccentric Fixation by the Bjerrum Screen. G. Brockbank and R. Downey.
Lesions of Ciliary Ganglion as a Cause of Argyll Robertson and Adie Pupils. M. E. Cameron.
Ocular Onchocerciasis in Northern Ghana. C. M. McLean.
Iodoacetate Poisoning of the Rat Retina II. Glycolysis in the Poisoned Retina. C. N. Graymore and K. Tansley.
A Bulbar Suction Test for Glaucoma. E. M. Evans and M. Klein.
Plasmoma of Conjunctiva. S. P. Mathur.
Removal of Elschnig's Pearls. D. H. Coop.
Diathermy Electrode. V. Preziosi.
Attachment for a Tudor Thomas Corneal Graft Stand. C. R. Kanagasundaram.
Book Reviews.
Notes.

Ophthalmic Literature.—Issued quarterly (£4 4s. annually; combined with *British Journal of Ophthalmology*, £9). The new issue is Vol. 13, No. 1.

British Journal of Ophthalmology.—Cumulative Index, Vols. 31-40, 1947-1956. Price 15s.

British Journal of Pharmacology and Chemotherapy.—Issued quarterly (£4 4s. annually). The new issue (Vol. 14, No. 3) includes:

British Pharmacological Society: Summer Meeting, 1959.
Effects of Diacetyl Monoxime on Neuromuscular Transmission. H. Edery.
The Action of Tubocurarine on Ciliary Movement. A. S. Milton.
The Fate of Oxytocin in Male and Female Rats. M. Ginsburg and M. W. Smith.
Actions of Scorpion Venom on Skeletal Muscle. K. R. Adam and C. Weiss.
A Comparative Study of the Effects of Drugs on the Arousal System of the Brain. P. B. Bradley and B. J. Key.
The Analysis of Drug-induced Tremor in Mice. A. Ahmed and N. R. W. Taylor.
Ouabain-induced Ventricular Tachycardia and its Effect on the Performance and Metabolism of the Dog Heart. G. Fawaz and B. Tutunji.
The Pharmacology of the Ethanesulphonate Anion. P. J. Goodford and H. R. Ing.
Observations on the Substrate Specificity of Amine Oxidases. H. Blaschko and I. L. Chruściel.
The Effects of Loading Rats with Intravenous Isotonic Sodium Chloride on the Renal Response to Diuretics. R. Keeler and H. Schnieden.
Isolated Rabbit Atria with Sympathetic Nerve Supply. S. Huković.
Mechanism of Action of Oral Anti-diabetic Drugs. Ranita Aiman and Nirmala Chaudhary.
The Action of Antisympathomimetic Drugs on the Urinary Excretion of Adrenaline and Noradrenaline. B. G. Benfey, G. Ledoux, and M. Segal.
A Hypothesis Concerning the Effect of Cocaine on the Action of Sympathomimetic Amines. W. H. Macmillan.
The Cardio-active Principle in Spleen. L. B. Cobbin and R. H. Thorp.
The Action of Nitrophenols on the Pulmonary Ventilation of Rats. C. M. Grant.
The Pharmacology of a Molluscan Smooth Muscle. Betty M. Twarog.
The Effect of Nitrofurazone on Trypanosoma Rhodesiense Infections in Mice. J. R. Baker.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 26

Guy's Hospital.—At Physiology Lecture Theatre, 5 p.m., endocrine demonstration: Gigantism and Acromegaly.
●Hunterian Society.—At Talbot Restaurant, London Wall, E.C., 7 for 7.30 p.m., first dinner meeting. 8.30 p.m., Presidential Address by Mr. A. W. Badenoch: Drops of Water—Grains of Sand.
London University.—(1) At Birkbeck College, Malet Street, W.C., 6 p.m., special university lecture in psychology by Professor E. G. Boring (Harvard): Pattern of Modern Psychology—(iii) Current Trends in American Psychology. (2) At Physiology Lecture Theatre, University College, W.C., 5.30 p.m., special university lecture in physiology by Professor A. Fleckenstein (Freiburg): Isotopic Studies of Phosphorus Metabolism in Skeletal and Heart Muscle—(i) Metabolism of Labile Phosphate Compounds in Living Muscle, Studied with Radioactive Phosphorus and Paper Chromatography.
Manchester Medical Society: (1) Section of Odontology.—At Lecture Room, Dental Hospital, 4.30 for 5 p.m., Presidential Address by Mr. A. H. Hilton: Ne plus ultra. (2) Section of General Practice.—At Large Anatomy Theatre, Medical School, Manchester University, 8.30 for 9 p.m., Professor D. A. K. Black: Treatment of Renal Disease.
Postgraduate Medical School of London.—4 p.m., Dr. M. D. Milne: Disorders of Potassium Metabolism.
St. Andrews University.—At Demonstration Room, Department of Medicine, 4 p.m., Professor I. G. W. Hill: Consideration of Some Problems in Haemodynamics and Heart Failure.

Tuesday, October 27

British Postgraduate Medical Federation.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. W. Mayer-Gross: Psychological Action of Drugs and the Methods of its Investigation.
Leeds Neurological Sciences Colloquium, 1959-60.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Sir Geoffrey Jefferson, F.R.S.: Basis of Consciousness.
●Liverpool University: Department of Extra-mural Studies.—At Medical School, Ashton Street, 7.30 p.m., Dr. G. F. Somers: Development, Methods of Testing, and Actions of Tranquillizing Drugs.
Postgraduate Medical School of London.—4 p.m., Dr. E. H. Belcher: Detection and Measurement of Radiation and Radio-isotopes—I.
Royal Army Medical College.—5 p.m., Dr. A. M. Cooke: Medical Writing.
Royal College of Surgeons of England.—5 p.m., Arris and Gale Lecture by Dr. K. M. Backhouse: The Gubernaculum Testis Hunteri, Testicular Descent and Maldescent.
Royal Statistical Society: Medical Section.—At Manson Theatre, London School of Hygiene and Tropical Medicine, 5.30 p.m., Mr. W. Haenszel (Maryland, U.S.A.): Some Problems in the Estimation of Familial Aggregation of Disease.
St. Mary's Hospital Medical School.—At Wright-Fleming Institute, 5 p.m., Mr. M. P. Embrey: Tocographic Study of Uterine Mobility.
University College London.—At Anatomy Theatre, Gower Street, W.C., 1.15 p.m., Dr. Elizabeth M. Deuchar, Ph.D.: How Embryos Develop: Grafting Experiments and the Organizer Concept.

Wednesday, October 28

Edinburgh University.—At Anatomy Lecture Theatre, University New Buildings, Teviot Place, 5 p.m., Inaugural Lecture by Professor J. S. A. Spreul, Ph.D.: The Veterinary Surgeon in General Practice.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Skin Cancer.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. F. H. Scadding: Intrathoracic Cysts.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. H. G. Hanley: Tuberculous Infections of the Urinary Tract.
LIVERPOOL SOCIETY OF ANAESTHETISTS.—At Liverpool Medical Institution, 8 p.m., Dr. Colin Ogilvie: Assessment of Respiratory Disability.
LONDON UNIVERSITY.—At Physiology Lecture Theatre, University College, W.C., 5.30 p.m., special university lecture in physiology by Professor A. Fleckenstein (Freiburg): Isotopic Studies of Phosphorus Metabolism in Skeletal and Heart Muscle—(ii) Turnover Rates of High Energy Phosphate Compounds During Activity and Rest as Indicated by the Oxygen Exchange with H_2O^{18}.
MANCHESTER MEDICAL SOCIETY: SECTION OF MEDICINE.—At Large Anatomy Theatre, Medical School, Manchester University, 4 for 4.30 p.m., Professor S. Alstead: Therapeutics, Medicine, and the Future.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor R. A. McCance: Chemical Stability in the Newborn Period.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Arnott Demonstration by Mr. D. Greer Walker: John Hunter—Order out of Variety.
ROYAL FREE HOSPITAL.—5.30 p.m., Dr. Klaus Schwarz (U.S.A.): Experimental Necrotic Liver Injury.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Lieutenant-Colonel J. Edmundson: Physical Education and the Adolescent (illustrated).
ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 2.30 p.m., Dr. W. W. Park: Embolism within the Pulmonary Circulation.

Thursday, October 29

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. J. H. Wilkinson: Blood Enzymes in Diagnosis.
HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Professor J. I. P. James: Early Treatment of the Injured Hand.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. R. Vickers: Dermatitis in Industry.
LIVERPOOL MEDICAL INSTITUTION.—5.15 p.m., History of Medicine Lecture by Sir Ernest Finch: Romance of Surgery.
NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, 8.30 p.m., Dr. R. L. Vollum: Antibiotics in Current Practice.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Thomas Vicary Lecture by Mr. H. R. Thompson: Serjeant Surgeons to Their Majesties.
ROYAL EYE HOSPITAL.—3.30 p.m., Dr. T. H. Whittington: Clinical Application of the Optical Principles of Retinoscopy.
ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Dr. I. E. Bush: Use of Chromatography for Estimating and Identifying Substances of Biological Interest.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. J. Hamilton Paterson: demonstration in neurology.
UNIVERSITY COLLEGE LONDON: FACULTY OF LAWS.—At Eugenics Theatre, Gower Street, W.C., 5 p.m., Mr. B. Hargrove, LL.M.: Revision of the Law Relating to Mental Health.

Friday, October 30

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. B. Mitchell Heggs: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. Lloyd Rusby and Mr. T. Holmes Sellors: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. Wallace Black: Vasomotor and Allergic Rhinitis.
INSTITUTE OF NEUROLOGY.—5.30 p.m., Dr. Paul C. Bucy (Chicago): Neural Mechanism Responsible for the Control of Motor Activity.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 4.30 p.m., Miss D. M. Shotton: An Emergency Maternity Service—the Place of the Flying Squad.
PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields, 8.30 p.m., Mr. G. Lloyd-Roberts: Common Orthopaedic Problems in the Young.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. A. Parks: Aetiology and Treatment of Fistula-in-Ano. (2) 4 p.m., Professor J. E. Squire: Phenylketonuria.
SOCIETY FOR ANALYTICAL CHEMISTRY.—At Cathedral Hotel, Salisbury, 7.45 p.m., joint meeting of Western Section of Society with Mid-Southern Counties Section of Royal Institute of Chemistry. Sir Charles Dodds, F.R.S.: Chemical Analysis and Clinical Diagnosis.

Sunday, November 1

COLLEGE OF GENERAL PRACTITIONERS: YORKSHIRE FACULTY.—At Littlewood Hall, General Infirmary at Leeds, 11.30 a.m., Mr. Daintree Johnson: Diagnosis and Management of Dyspepsia.
DENTAL AND MEDICAL SOCIETY FOR THE STUDY OF HYPNOSIS: MIDLAND BRANCH.—At Birmingham Medical Institute, 6 p.m., Mr. Leonard Becker: Hypnosis in Dentistry.
MANCHESTER UNIVERSITY: FACULTY OF MEDICINE AND COLLEGE OF GENERAL PRACTITIONERS: NORTH-WEST ENGLAND FACULTY.—At Theatre 1, Clinical Sciences Building, York Place, 11 a.m., Mr. D. Lloyd Griffiths: Backache.
UNIVERSITY COLLEGE HOSPITAL.—10.15 a.m., meet in Front Hall of main Hospital. Lecture-demonstration for general practitioners. Mr. D. R. Davies: Nocturnal Enuresis and Incontinence.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—L. H. Pimm, F.R.C.S., Consultant Orthopaedic Surgeon, Ipswich and East Suffolk Hospital Group; B. W. Orchard, M.B., B.S., D.P.M., Assistant Psychiatrist, Hellesdon Hospital; M. F. Terry, M.B., B.S., Registrar in Obstetrics and Gynaecology, Ipswich and East Suffolk Hospital Group; J. T. F. Keohane, M.B., B.Ch., B.A.O., Ear, Nose, and Throat Registrar, Norfolk and Norwich Hospital and Jenny Lind Children's Hospital, Norwich.

FLEMING, CHARLES, M.B., Ch.B., D.P.H., Deputy County Medical Officer, Fife.

GRAINGER, R. G., M.D., F.F.R., M.R.C.P., D.M.R.D., Consultant Radiologist to United Sheffield Hospitals.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—M. Nicholls, M.B., B.S., Assistant Resident Medical Officer, Tadworth Court, D. A. Cotton, M.B., Ch.B., and Jane G. Jenkinson, M.B., B.S., D.C.H., House-physicians; A. D. Courtemanche, M.D., House-surgeon to Orthopaedic and Plastic Departments; Barbara E. Clayton, M.D., Ph.D., Consultant Pathologist in charge of Departments of Chemical Pathology; Kenneth Till, M.B., B.Chir., F.R.C.S., Consultant Neurosurgeon; Anne C. Metten, M.B., Ch.B., D.C.H., and V. R. Bloom, B.M., B.Ch., House-physicians; C. D. Hierons, M.B., B.S., House-surgeon; E. Bettio, M.D., Resident Officer to Neurological and Neurosurgical Department; H. Taylor, M.D., and F. M. Elderkin, M.B., B.S., M.R.C.P.Ed., D.C.H., House-physicians; J. D. Ellis, M.B., B.Chir., and G. V. P. Chamberlain, M.B., B.S., D.Obst.R.C.O.G., House-surgeons; Elinor J. Guthrie, M.B., B.Ch., Assistant Resident Medical Officer, Tadworth.

LEEDS REGIONAL HOSPITAL BOARD.—A. A. Driver, M.D., D.P.H., Senior Administrative Medical Officer.

LIVERPOOL REGIONAL HOSPITAL BOARD.—J. R. Gibson, Ph.D., M.B., Ch.B., D.P.H., Deputy Senior Administrative Medical Officer.

MANCHESTER REGIONAL HOSPITAL BOARD.—P. J. D. Snow, M.D., M.R.C.P., Consultant Physician (eight half-days weekly), Bolton and District Group of Hospitals; G. H. Waddington, M.R.C.S., L.R.C.P., D.M.R.D., Whole-time Consultant Radiologist at Lancaster and Kendal and Lancaster Moor Groups of Hospitals; B. L. Williams, M.B., Ch.B., D.Path., Whole-time Consultant Pathologist to West Manchester Group of Hospitals; L. R. McLaren, M.B., B.Chir., F.R.C.S., maximum part-time Consultant Plastic Surgeon to South Manchester Group of Hospitals, etc.

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—W. Jones, Williams, M.D., Consultant Pathologist, Mount Vernon Hospital; J. G. Sommerville, M.D., Consultant Physician in Physical Medicine, Medical Rehabilitation Centre and Paddington General Hospital; D. L. B. Farley, M.B., B.S., F.R.C.S., Consultant Surgeon, Royal Northern Hospital and Highlands General Hospital; Beryl M. Goetzee, M.B., B.S., F.F.A. R.C.S., and Christine B. A. John, M.B., Ch.B., F.F.A. R.C.S., Consultant Anaesthetists, Royal London Homoeopathic Hospital; Kathleen M. Witham, M.R.C.S., L.R.C.P., D.Obst.R.C.O.G., D.C.H., Consultant Dermatologist, Luton Hospitals; D. C. Beatty, M.D., M.R.C.P., D.Phys.Med., Consultant Physician in Physical Medicine, St. Albans City Hospital, Victoria Hospital, Welwyn, Harpenden Memorial Hospital; D. E. Hone, M.B., B.Ch., D.O., Ophthalmologist (S.H.M.O.), St. Pancras School Treatment Centre; P. Timmis, M.B., B.S., F.R.C.S., Consultant Ear, Nose, and Throat Surgeon, Luton and Hitchin Group of Hospitals; P. J. Hare, M.D., M.R.C.P., Consultant Dermatologist, Whittington Hospital; J. E. A. O'Connell, M.S., F.R.C.S., Consultant Neurosurgeon, Luton and Dunstable Hospital; R. M. Gabriel, L.R.C.P.&S.Ed., D.P.M., Assistant Child Psychiatrist (S.H.M.O.), Hertfordshire Child Guidance Service; Irene D. R. Gregory, F.R.C.S., D.O.M.S., Consultant Ophthalmologist, Royal London Homoeopathic Hospital; E. P. G. Michell, M.B., M.R.C.P., D.C.H., Consultant Child Psychiatrist, Tavistock Clinic; Una O'Connell, M.B., B.S., D.M.R.D. Consultant Radiologist, Clare Hall Hospital; R. W. McNabb, M.R.C.S., L.R.C.P., D.M.R.D., Consultant Radiologist, Watford Hospitals; K. W. G. Heathfield, M.D., M.R.C.P., Consultant Neurologist, Barnet General Hospital; Clara L. Gough, M.B., Ch.B., Assistant Psychotherapist (S.H.M.O.), King Edward VII Hospital, Windsor.

WELSH BOARD OF HEALTH.—T. T. Baird, M.B., B.Ch., D.P.H., Senior Medical Officer.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Anderson.—On September 21, 1959, William Beveridge Anderson, L.R.C.P.&S.Ed., L.R.F.P.S., of 23, Stonegate, and Bootham Park, York, late of India.

Beveridge.—On September 25, 1959, in Venice, Italy, Arthur Joseph Beveridge, C.B., O.B.E., *M.C.*, M.Sc., M.B., B.Ch., D.P.H., Major-General, late R.A.M.C., retired, of 33, Belgrave Square, Rathmines, Dublin, aged 66.

Breslauer.—On September 20, 1959, at Meanwood Park Hospital, Leeds, Yorks, Hans Breslauer, M.D., aged 63.

Bryant.—On September 19, 1959, at Barn Fields, Copsale, near Horsham, Sussex, Charles Hilary Bryant, M.D., F.R.C.S.

Elliott.—On September 29, 1959, at Bryn-y-Forwyn, St. Davids, Pembs, Joseph Haslett Elliott, *M.C.*, M.D.

Gibb.—On September 18, 1959, at Southampton, Hants, John Joseph Gibb, M.B., Ch.B.

Hoogewerf.—On September 28, 1959, at his home, Woodstock, St. Paul's Wood Hill, Orpington, Kent, Bernard Albert Hoogewerf, L.M.S.S.A., Major, I.M.S., retired.

Ironside.—On September 21, 1959, at Cromer, Norfolk, Reginald William Ironside, M.B., B.Ch., F.F.A. R.C.S., of 110, St. James's Court, London, S.W., and Highlands, Esher, Surrey.

Lansdown.—On September 23, 1959, at Lymington Hospital, Robert Blake Poole Lansdown, M.B., B.Ch., of Tree Tops, Fairfield Close, Lymington, Hants.

Levy.—On October 2, 1959, Abraham Leo Levy, M.B., Ch.B., of 92, Bignor Street, Manchester.

McPherson.—On September 17, 1959, at Bradford Royal Infirmary, Barbara McPherson (formerly Simonds), M.B., B.Chir., of Fourways House, Hoddesdon, Herts.

Melhuish.—On September 22, 1959, Herbert Michael Henry Melhuish, D.S.O., M.R.C.S., L.R.C.P., D.P.H., Lieutenant-Colonel, I.M.S., retired.

Metcalfe.—On September 22, 1959, in a nursing-home, Brighton, Sussex, Thomas Marshall Metcalfe, L.R.C.P.&S.Ed., L.R.F.P.S., of 46, Park Crescent, Brighton.

Morris.—On October 2, 1959, in hospital, Hugh McEvoy Morris, M.D., D.M.R.E., of St. John Street, Manchester.

Moss.—On September 22, 1959, at Firgrove, Cape Province, South Africa, Adam Moss, M.D., late of West Kirby, Cheshire, aged 90.

Tilbury.—On September 21, 1959, Robert Tilbury, M.R.C.S., L.R.C.P., of 41, Wildcroft Manor, London, S.W.

Satow.—On September 29, 1959, at Westacott, Honeychurch, North Tawton, Devon, Lawrence Lancaster Satow, *M.C.*, M.R.C.S., L.R.C.P.

Slaney.—On September 19, 1959, at 145, Otley Old Road, Leeds, Yorks, Robert Slaney, L.R.C.P.&S.I. and L.M.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Persistent Threadworms

Q.—*A family is infested with threadworms. In spite of all precautions and treatment, the infestation persists. The father runs a small mink-farm close to the house. Could this be a possible source of the infestation?*

A.—No animal is necessary for the transmission of the human threadworm, *Enterobius vermicularis*, which has not been reported in animals. The presence of the animals on the farm cannot therefore be incriminated as a cause of persisting infection in this family. The precautions taken as well as the type and timing of treatment should be reviewed.

Perpetuation of infection is often the result of scratching the perianal skin, on which the female worm lays eggs during the night and causes pruritus by so doing. Eggs are then transmitted on fingers, and particularly behind the nails, to food and the mouth, and after being swallowed develop into mature worms. It is therefore important to break this vicious circle whereby pruritus caused by the worm leads to scratching and contamination of fingers and the latter to further infection. The most important means of so doing consists in keeping the nails well trimmed and cleaned and scrubbing them and the hands after each visit to the toilet and before every meal. A bath taken on rising in the morning will also assist by washing eggs away before they can contaminate day clothing. Various investigations have shown that dust in houses becomes contaminated with eggs and may give rise to chronic light infections. The dust in bedrooms and in beds slept in by infected persons contains most eggs, but their number can be reduced by infected persons wearing closely fitting underpants at night, and it has further been suggested that they should not sleep with their head underneath the bedclothes.

Piperazine is the most satisfactory drug for treatment of threadworm infections, and it is important that all members of the family should be treated simultaneously in cases such as here reported. Unless this is done the untreated member or members may reinfect those who have been treated.

Poliomyelitis Vaccine and Vision

Q.—*Three patients who were reliable witnesses reported a temporary loss of accommodation, as evidenced by their inability to read print or do close work, on the evening of the day on which they had had their poliomyelitis inoculation. Is this of any significance?*

A.—Many millions of doses of poliomyelitis vaccine have now been given and serious reactions have not been reported. Allergic skin reactions occur, but even these are rare. I know of only one case in which blurring of vision occurred on the evening of a poliomyelitis injection in a hospital employee, but he had similar reactions after every immunization procedure and they were therefore regarded as being psychogenic. An injection of poliomyelitis vaccine seems to provoke considerable emotional response, especially among young adults, and this would have to be considered as a possible explanation in the present case. On the other hand, neurological complications, usually severe, have occurred after several immunization procedures —e.g., anti-pertussis and T.A.B. vaccines. One can say only that loss of accommodation does not appear to have been reported after poliomyelitis inoculation. Poliomyelitis is a dead vaccine and therefore toxaemia cannot occur. The condition as described would not appear to have any significance.

Chemotherapy in Sonne Dysentery

Q.—*Since the organisms responsible for Sonne dysentery are now resistant to sulphonamides, is neomycin an effective and safe alternative? Is it necessary to do sensitivity tests on each individual case?*

A.—*Shigella sonnei* is nowadays often, but not always, sulphonamide-resistant. Alternatives (all administered orally) are streptomycin, neomycin, the tetracyclines, and chloramphenicol. It is wise to verify sensitivity before depending on one of these, although resistance to neomycin is rare. Sonne dysentery is often epidemic, and when this is so the findings in one case may be assumed to apply to others. It is arguable whether mild cases of this infection merit any such treatment.

Photography on the Round

Q.—*What is the most suitable apparatus to carry around in general practice for taking impromptu colour photographs of skin conditions?*

A.—Most skin conditions need to be photographed in "close-up." The expensive answer to doing this conveniently is to use a 35-mm. reflex camera which is fitted with a preset aperture diaphragm and extension tubes. This enables the camera to be held in the hand, focused at full aperture by adjusting the distance of the camera, and the aperture will close itself to a preset value as the release button is pressed. Lighting is by means of expendable flash bulbs. The flash gun should be mounted on the camera and synchronized to it. Only if large numbers of pictures are taken is it worth investing in an electronic flash outfit.

A cheap 35-mm. camera can be quite satisfactory if it is fitted with a rod-and-frame mechanism which is used with a supplementary close-up lens. The frame is merely placed over the area to be recorded and the exposure made. No view-finding or focusing is necessary. The lighting again is by expendable flash bulbs. Exposure for both types of apparatus is determined for a few standard distances, and, provided these are adhered to, constant results will be obtained.

Alcoholic Hangover

Q.—*In "Any Questions?" (January 24, p. 97) you suggest that any remedy for motion sickness be tried for alcoholic hangover. What is the rationale of this? Would hyoscine be as good as cyclizine?*

A.—The nausea and vomiting of alcoholic intoxication are partly due to an alcoholic gastritis and partly due to a central action of the drug on the nervous system. Nausea, vomiting, and all the symptoms of a "hangover" may follow the intravenous infusion of alcohol. One of the actions of certain of the antihistamine group of drugs—e.g., dimenhydrinate—is to depress the activity of the vomiting centre. This is shown by their ability to lessen the frequency of apomorphine-induced vomiting in dogs. It is this central anti-emetic activity of the antihistamines which might be of value in the treatment of an alcoholic hangover. The anti-emetic property of hyoscine is presumably due to a similar action and it might be equally effective, but, when given orally, hyoscine does not have the same general sedative effect as the antihistamines.

Herpes by the Seaside

Q.—*Is it common for herpes labialis to appear about four days after a person arrives at the seaside? How might it be prevented?*

A.—It is common for recurrent herpes to be activated by exposure to sunlight or excitement, and both may play a part in herpes simplex, especially about four days after the subject arrives at the seaside.

There is no specific treatment for this common complaint, and the rational method of increasing specific herpetic

antibodies by vaccine therapy seems less reasonable when it is known that many subjects carry specific antibodies in their blood and the titre of these antibodies is often not affected by a further eruption of recurrent herpes.

Sedative doses of *x* rays, about 100 to 150 r repeated in two to three weeks' time for three exposures, sometimes break this cycle of recurrent herpes. There is some evidence that nicotinamide (50 mg.), taken three times a day at the onset and continued once a day for three or four weeks after the attack, diminishes the tendency to relapse. Finally, complete protection from direct sunlight is desirable but may be difficult to achieve. Eradication of any focus of sepsis or irritating metallic fillings has been followed by permanent relief in some subjects.

Transplantation of Ovary

Q.—*I have under my care a girl of 20 who had to have both ovaries removed because of dermoid cysts. Are there cases on record of successful transplantation of the ovary?*

A.—Transplantation of ovarian tissue from one site to another in the same person is recorded with a considerable degree of success. In the early part of this century fragments of ovary recovered from appendages removed for chronic inflammatory or other diseases were, at the conclusion of the operation, often implanted into the rectus abdominis muscle, the omentum, or the cellular tissues of the broad ligament and labium majus. In a high proportion of cases these maintained their endocrine function for many years but did not, of course, restore fertility. The literature covering this subject was reviewed by F. H. Martin[1] and W. Blair-Bell.[2] Although C. L. Buxton and Ada S. H. Wong[3] and M. Blanc[4] advocated it more recently, the procedure is now rarely practised because its objective can be largely achieved by the administration of synthetic or natural hormones.

There is no known record of transplanting an ovary from one individual to another successfully. Nor is it likely to be practicable at present, although work which is proceeding in other fields suggests that it might become feasible in the future. If it does, restoration of fertility in the sort of case mentioned in the question would require not merely toleration of a foreign organ by the host but the vascularization and survival of the grafted ovary in a position which would allow its ova free passage to the tubes and uterus—a project presenting many technical problems.

It may be added that the tragic situation indicated by the question is now unusual because it is recognized that dermoid cysts do not destroy ovarian tissue; they merely displace it. It is therefore nearly always possible to conserve the ovary by performing "cystectomy" rather than "ovariotomy."

References

1 Martin, F. H., *Trans. Amer. gynec. Soc.*, 1922, **47**, 11.
2 Blair-Bell, W., *Surg. Gynec. Obstet.*, 1925, **41**, 706.
3 Buxton, C. L., and Wong, A. S. H., *Amer. J. Obstet. Gynec.*, 1950, **60**, 401.
4 Blanc, M., *Gynéc. et Obstét.*, 1950, **49**, 360.

Organic Brain Disease and Dreams

Q.—*May the content of dreams indicate organic brain changes? Could one, for instance, correlate certain dreams with arteriosclerotic changes, and dreams of a different type with a localized tumour of, say, the island of Reil?*

A.—This is not an easy question to answer, for the content of dreams depends to a large extent on the individual's personality, fears, repressions, and so on. In elderly patients, who may be suffering from arteriosclerotic changes, the remote memory is better preserved than the more recent, and perhaps as a result of this they may be distressed by nightmares about episodes in early life which they had otherwise largely forgotten.

Damage to the brain in the parieto-occipital region may abolish dreaming entirely, and this is probably due to the fact that the mechanism of dreaming depends on visual memories, but in this connexion I am unable to say what is the dream content of those who are born blind.

Epileptic fits beginning in the temporal lobe sometimes cause forced thoughts of a certain type in a conscious patient, but I have not come across any case in which this was remembered subsequently as a dream, the attack having occurred in sleep. It seems likely, therefore, that the only effect of organic disease of the brain on dreaming will either be to abolish it or to increase the likelihood of early dreams to come back through the disappearance of more recent memories.

Ichthyosis Simplex

Q.—*A woman aged about 45 years, in good health, has always suffered from dry skin (two near relatives have the same complaint). The whole body is affected and one or two small patches look almost like an ichthyosis. The skin looks as if powder had been applied to it, and on lightly rubbing this falls off in a small cloud. What is the diagnosis and treatment?*

A.—This condition is probably ichthyosis simplex, a condition which affects almost the whole body but spares the axillae, the perineum, the antecubital region, and the popliteal region. It is often associated with some degree of follicular keratosis and atrophy of the hair. It is well recognized that this is one of the most common inherited defects of the skin, though it may also arise without any family history, and it is inherited usually as an irregular dominant.

As with any inborn character, it is hardly susceptible of cure. In some cases it may be improved by the administration of large doses of vitamin A, but it is hardly desirable to continue such treatment over long periods. Usually patients can mitigate the effects of the disorder by applying creams or oily lotions to the skin, particularly after washing. The addition of glycerin to these is also beneficial. In some patients there is a deficiency of sweating, so that they become uncomfortable and even suffer heat stroke in warm weather or in tropical countries. More often, however, in a milder case, the condition improves in the summer.

Hypnosis for Obesity

Q.—*An attractive child of 13 years has a familial tendency to gross overweight. Could hypnosis be used in treatment, and what are the contraindications?*

A.—Hypnosis could be used in the treatment of a fat child to reduce the appetite and increase the determination to diet strictly. Alternatively it could be used to make the child accept her stoutness without self-consciousness and to diminish embarrassment. There are no medical contra-indications to the use of hypnosis, but to use it for treating obesity is unusual.

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